# ERNATIONAL MEDICAL DIGEST

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# General Medicine

**ureomycin Therapy of Nonpneumococcic and Nontuberculous Bacterial Pulmonary Infections** — COLLINS, HARVEY SHIELDS, GOCKE, THOMAS M. AND FINLAND, MAXWELL — *Archives of Internal Medicine*, 84: 875 (December) 1949.

The writers present the results of aureoycin therapy in cases of the nonpneumoccic and nontuberculous bacterial infecns of the lungs.

"Two groups of cases were studied and eated. Group I includes 13 patients with ute pneumonia in whom cultures of utum obtained before any therapy was ven yielded predominant or pure growths pathogenic bacteria other than pneumocci. Most of these patients had an antedent illness which was consistent with e diagnosis of 'clinical influenza' and nich occurred during March 1949, when oved influenza virus infections were evalent in this community. None of these tients had received any antimicrobial ents before the administration of aureoycin was started, and they were acutely , with physical and roentgen signs of eumonia at the time. Four of these paents were treated in nearby hospitals, d the others were from the medical ards of the Boston City Hospital. Group includes 20 patients with infections that n best be characterized as 'nontuberculs bronchopulmonary suppuration.' nese patients were all from the adult edical wards of the Boston City Hospital. l but 1 of them had been treated with rge doses of other antimicrobial agents r varying periods before aureomycin erapy was started and had obtained only mporary benefit or none at all from the evious therapy. They were all acutely ; some of them were also chronically ill, d all but 5 were febrile at the time aureoycin was started. In each case, pathonic bacteria other than pneumococci ere obtained in abundance or in pure growth from cultures of the sputum before the use of aureomycin was started."

"Almost all the aureomycin was given by mouth in the form of capsules, each containing 250 mg. of the crystalline hydrochloride, but occasional patients received some or all of the oral doses of the antibiotic in the form of the aureomycin base. One patient received only intravenous injections of aureomycin hydrochloride, 500 mg. daily in 1,000 or 1,500 cc. of a 5 per cent solution of dextrose in water, and a second patient received similar therapy for four days, after which he was treated orally. The dosage used to initiate the oral therapy in the patients of both groups was as follows:

| | Number of Patients | |
|---|---|---|
| Starting Dosage | Group I | Group II |
| 1.0 Gm. every 4 hours... | 5 | 11 |
| 1.0 Gm. every 6 hours... | 4 | 2 |
| 0.5 Gm. every 4 hours... | 2 | 6 |
| 0.5 Gm. every 6 hours... | 2 | .. |

This dosage was later revised in many instances, the larger doses being reduced after the patient improved or if there was intense vomiting and the smaller doses increased if the patient did not improve promptly."

Acute Bacterial (Nonpneumococcic) Pneumonia.—"The patients were mostly young adults, but 4 of them were 60 to 76 years old; 8 of the 13 were men. The predominant organism isolated from the pretreatment sputum was either a beta hemolytic streptococcus, hemolytic *Staphylococcus aureus* or both in 11 of the patients; a hemolytic streptococcus and *Klebsiella pneumoniae* (Friedländer's bacillus) type A in 1 patient and *Hemophilus influenzae* in another. All the blood cultures taken in these cases yielded no growth."

There was among these 13 patients definite evidence of influenza virus infection in 5 patients (4 with A and 1 with B

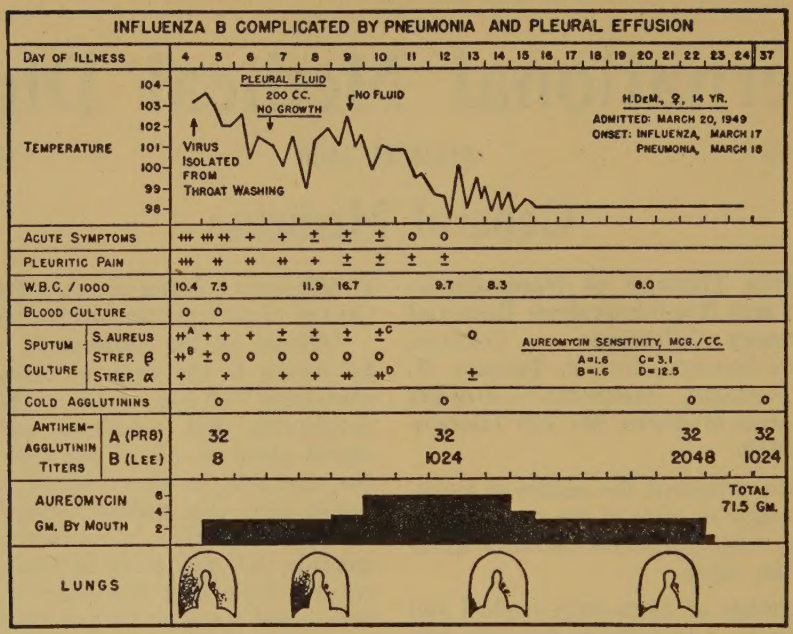


Chart 1.—Course, treatment and relevant laboratory data in case 1.

organisms), titers strongly suggestive of similar recent infections in 4 others (3 with A and 1 with B organisms) and possibly in 2 additional cases (both with B organisms).

"Tests for cold agglutinins and for Streptococcus MG agglutinins were carried out in serums taken before treatment was started and at intervals thereafter in all but 1 of these patients. . . . The results of these tests, together with those for influenza antibodies, were interpreted as offering no support for the diagnosis of primary atypical (virus) pneumonia in any of these patients."

"Treatment with aureomycin was begun during the first three days of the pneumonia in 8 cases, on the fourth or fifth day in 3 and on the sixth or seventh day in the remaining 2 cases. . . . All the patients were acutely ill and febrile when the first dose of aureomycin was given. The temperature at this time ranged between 101 and 105 F. and was 103 F. or higher in 10 of the 13 patients. The total leukocyte counts varied between 4,300 and 16,100, and in 9 of the patients these counts were below 12,000.

"The pulmonary lesion as determined by physical examination and from the roentgenograms was limited to a single lobe in 10 cases and to two contiguous lobes of the right lung in 2 cases; it was bilateral in only 1 case. In most of the cases the lesions appeared in the roentgenograms as mottled or patchy areas of density with predominantly peribronchial distribution or radiating out from the hilar region. In 4 cases, however, the physical and roentgenographic signs were those of lobar consolidation similar to those characteristically found in pneumococcic pneumonia. There were also musical rales heard bilaterally in most of the cases and showers of crepitant rales over the consolidated areas. Most of the patients had severe cough and complained of soreness over the sternum, but several complained of pleuritic pain and a loud friction rub was heard in 5 patients.

"An attempt was made to estimate the severity of the illness in each case from the general appearance of the patients, the symptoms and other observations. The illness at the time aureomycin was started was considered to be severe in 5 cases, moderate in 7 and mild in 1."

"One of the patients who had a complicating pleural effusion received a total of 71.5 Gm. in 18 days (case 1, chart 1). The total dose for the remaining 12 pa-

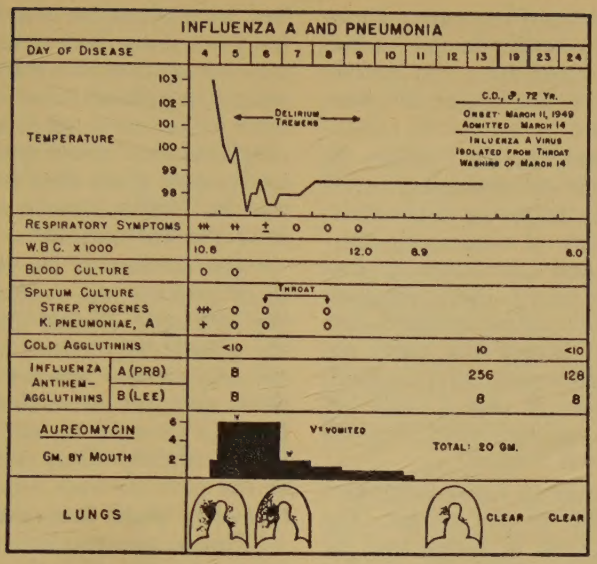


Chart 2.—Relevant data in case 2.

nts ranged between 6 and 24 Gm. and as given over a period of two to seven ys. The average total dose of these 12 tients was 13.3 Gm. in an average of ur and one-half days. One patient re-ived four daily doses of 500 mg. of reomycin intravenously, and oral doses re used to continue the therapy in this se.

"A major drop in the temperature oc-rred, except in case 1, in the first 12 24 hours, and only 2 patients had any ver after the second day of therapy. In se 1 there was a sterile pleural effusion d the temperature dropped gradually ring the first three days, but this was llowed by a second bout of fever, lasting ur more days." In 1 case there was inter-ittent fever associated with pyrogenic re-tions to intravenous injections during e second and fourth days.

"Symptomatically, all the patients were oticeably improved by the end of the st 24 hours; 10 were entirely free of mptoms by the end of the second day, d the remaining 3 continued to have euritic pain, raise blood-tinged sputum had other minor complaints for three, x and seven days, respectively, after reomycin was started.

"The lungs cleared rapidly, as judged the physical and roentgen observations. There was definite evidence of clearing of the lungs in all but 2 of the patients within the first four days. The lungs were entirely clear roentgenographically by the end of a week after the first dose in 10 patients." In case 1, in which there was a pleural effusion; in another case in which there was atelectasis of the middle lobe of the right lung, and in case 2 (chart 2), in which there was probably some abscess formation in the upper lobe of the right lung, complete clearing of the pulmonary fields roentgenologically was delayed until 14 to 16 days after the use of aureomycin was started.

"The predominant organisms found in the sputum were rapidly cleared after the start of aureomycin treatment, although the results in some cases were not so striking as they were in all cases of pneumococcic pneumonia. Cultures of sputum were made at frequent intervals during and after treatment in 9 of the cases. Hemolytic streptococci present in the sputum before treatment could no longer be demonstrated after the first day of aureomycin therapy in 4 cases and after the second, third and fourth day in 1 case each." In 1 case the hemolytic streptococci were still present in cultures of the sputum after seven days of therapy. "There were 2 patients who continued to raise rusty sputum, 1 for 4

days and the other for 6 days after aureomycin was started; hemolytic streptococci could not be recovered from the sputum after the first day in the former and after 3 days in the latter.

"Hemolytic *Staph. aureus,* present in large numbers in the cultures made before treatment, could no longer be demonstrated after the first day of aureomycin therapy in 1 patient and after three or four days in 4 others. In case 1, these organisms were obtained in diminishing numbers during seven days of therapy but could not be obtained from subsequent sputum specimens. *K. pneumoniae* in case 2 could not be recovered from any specimens obtained after aureomycin was started."

Tests for sensitivity to aureomycin were carried out on most of the strains. The hemolytic streptococcus in 1 case was the least sensitive of the strains tested and required 12.5 micrograms for complete inhibition. "*K. pneumoniae* was sensitive to 6 micrograms, and all other strains of hemolytic streptococci and staphylococci were completely inhibited by 3 micrograms or less. The sensitivity of all strains of the same organisms isolated from the same patient after aureomycin therapy was started was the same as before the start of treatment, and no evidence of increase in resistance could be found in any of the strains from this group of patients.

"Nontuberculous Pulmonary Suppuration.—The second group consists of 20 cases of the type in which the results of therapy at best are very difficult to evaluate. The patients ranged in age from 37 to 78 years, and only 5 were less than 50 years old. All but 3 of the patients were male. There was a history of underlying productive cough for varying periods in almost all these cases, and other serious underlying conditions played a significant or major role in most of them.

"In almost all these cases the treatment with aureomycin was undertaken during an exacerbation of the chronic underlying bronchopulmonary infection, usually following some acute infection of the upper respiratory tract or pneumonia. The history of the underlying respiratory disease was usually long and complicated and many forms of therapy had been used." During the acute episode, except in 1 case, treatment with other antimicrobial agents had been given for varying periods ranging from three days to several months before aureomycin was started. "Aureomycin was given in these cases for varying periods while either some other agents were being continued or some other antimicrobial agents were given after it became apparent that no further benefit could be expected from the aureomycin."

"The severity of the disease in each of these patients was graded on the basis of the available clinical findings and from the general appearance at the time when aureomycin was started. Six of the patients were considered to be moderately ill; 10 were severely ill, and 4 were thought to be critically ill at the time. All but 5 of the patients were febrile, and most of them had slight to moderate leukocytosis.

"The pulmonary lesion in most of the cases consisted of rather diffuse areas of patchy density in both lungs, particularly in the bases. There was also evidence clinically of chronic bronchitis and bronchiectasis in most of the cases. In a few cases there were large solitary or multiloculated abscess cavities in a single lobe with pneumonitis in the surrounding lung, and fluid levels within the cavities were visualized in the roentgenograms from time to time in such cases."

"All the blood cultures taken before administration of aureomycin was started showed no growth."

"The bacterial flora in the sputum of the patients varied considerably, but in most of them there were one or two organisms which were predominant in the pretreatment cultures. Coagulase-positive strains of hemolytic *Staph. aureus* were the most frequent; these strains were all highly resistant to penicillin, the patients having previously been treated with massive doses of this antibiotic. Most of these strains of staphylococci were susceptible to aureomycin, being completely inhibited by 3 micrograms per cc. or less, but two of them required 6 micrograms and one required 25 micrograms for complete inhibition. Hemolytic streptococci in large numbers were isolated from 3 patients and *Hemophilus influenzae* from 2 others; all these strains were sensitive to 3 micrograms per cc. or less.

"There were 2 cases of type A *K. pneumoniae* pneumonia in this group. In both

them streptomycin and penicillin had en used before the aureomycin was start- l; in 1 of them the organisms were no nger demonstrable in the blood, and in e other they could not be obtained from ltures of the sputum after aureomycin as started. In each of the 2 cases there as extensive abscess formation which ap- ared to be progressing, and both patients ere still acutely ill when aureomycin erapy was started." The strains of *K. neumoniae* from both of these patients ere highly sensitive to streptomycin be- re that antibiotic was given, and the rain isolated before aureomycin treat- ent in 1 case was just as sensitive to reptomycin as the original strain in that se.

"In the remaining cases the predominant rganisms were mainly of the type more equently encountered in chronic infec- ons of the urinary tract; namely, *Aero- cter aerogenes, Proteus vulgaris* and *seudomonas aeruginosa.* Most strains of ese organisms were moderately to arkedly resistant to aureomycin, requir- g 25 to 200 micrograms per cc. for com- ete inhibition."

In 1 case *Diplococcus pneumoniae* type was found in the initial sputum speci- en and was identified in smears and cul- res. "The pretreatment sputum speci- en, however, showed a predominance of am-negative bacilli, and *P. vulgaris* also redominated in the surface cultures of is sputum."

"Larger doses were used and were given er longer periods in these cases than in ose of group I. The total oral dose varied om 21 to 222 Gm. given over periods nging from 7 to 46 days. The patient ho received the largest amount was given reomycin intermittently for one to three eeks at a time over a period of several onths. In all the other cases the entire se was given more or less continuously." he intravenous route was used exclusively 1 case, 500 mg. being given daily for ght days. "The average oral dose in the maining 19 patients was 70 Gm. given er an average of 17 days."

Most patients showed some improvement their general condition soon after the reomycin was started, and in some of ose who were severely or critically ill the time the immediate improvement was dramatic. "The temperature usually declined slowly. The sputum, in those in whom it was foul, lost its odor in most cases. The amount of sputum raised was usually decreased markedly, and some of the patients stopped raising any sputum. The character of the sputum in other cases changed from purulent to mucoid.

"Improvement in the pulmonary lesion as judged from the physical signs and the roentgenograms also varied considerably. There was marked and fairly rapid clearing in some of the cases, but in most instances this occurred slowly. Surgical drainage of abscesses was required in only 2 of the cases, including 1 case of *K. pneumoniae* infection."

"Two of the patients died. In 1 case death resulted from hypernephroma and uremia, the latter already rather severe when the aureomycin was started. In this case there was marked improvement during the first two days of intravenous aureomycin therapy. In the other case death occurred almost a year after the patient received the first course of aureomycin. This patient was almost moribund when the aureomycin was first given, and she was noticeably improved for several weeks at a time during and after each course of aureomycin."

As for the effects of aureomycin treatment on the bacteriologic flora of the sputum the susceptible strains were cleared rapidly in most cases and somewhat more slowly in others. "In the majority of the cases relatively resistant organisms, usually *P. vulgaris, A. aerogenes* or *Ps. aeruginosa,* replaced the strains of sensitive organisms." Increase in resistance of strains of the same organisms isolated during or after the course of aureomycin was noted only in 1 case. "In this case aureomycin was given orally and was also instilled intrapleurally in increasing amounts over several weeks. After each intrapleural instillation the number of organisms in the exudate decreased markedly, as did the amount of exudate, but these changes were only temporary. In this case the strain of *A. aerogenes* when originally isolated was sensitive to 25 micrograms of aureomycin per cc., and the organisms obtained after several weeks required 100 micrograms for complete inhibition. In all other cases, all strains of the same organisms isolated

before, during and after aureomycin therapy had the same sensitivity to this antibiotic."

The untoward effects from aureomycin were limited almost entirely to gastrointestinal symptoms. "Vomiting or nausea occurred during oral therapy in 9 of the cases of group I and in 11 of those in group II. Loose and frequent bowel movements were experienced in a total of 5 cases in both groups, including those of 4 patients who also had gastric symptoms. There were also 2 cases in group II in which the patients complained of slight dizziness after more than a week of therapy. In a third case of this group the tongue appeared red and smooth at the end of a 31 day course. The last 3 patients also vomited several times during the latter part of their therapy. There were 4 cases in group I and 7 in group II in which the patients experienced no untoward effects whatever."

Among the patients who experienced nausea and vomiting from the aureomycin this was transient in some, occurred only after two or more days of therapy in others and in several was experienced only on the largest oral doses (1 Gm. every four hours) and did not occur after the dose was reduced to 0.5 Gm. every four hours. "Among those who had some untoward gastrointestinal symptoms were 9 patients who received more than one lot of aureomycin, each preparation being given for three to seven or more days in doses of 1 Gm. every four or six hours. Five of these patients had these symptoms from only one of two lots and not from the other; 1 patient had them from one of three and another from one of four lots and not from the other two and three, respectively. One additional patient received four lots, and another received six different lots; the former had untoward effects from two and the other from four of these lots."

The patient who received part of the aureomycin intravenously experienced mild pyrogenic reactions from the second and the fifth dose, but there were no reactions in 1 case in which all of the aureomycin was given intravenously. "One patient who received eight intramuscular injections of 100 mg. each during the first day had considerable local pain and tenderness." In 1 case there were no untoward reactions when small amounts of aureomycin were injected intrapleurally, but when 50 or 100 mg. was instilled the patient complained of a "hot sensation" in the chest that lasted several minutes.

"In no instance was there any fever or rash that could be attributed to the aureomycin. There were no detectable untoward effects on the blood, kidneys, liver and nervous system in any of the patients."

**Aureomycin Treatment of Pneumococcic Pneumonia. Clinical and Laboratory Studies on 33 Patients** — GOCKE, THOMAS M., COLLINS, HARVEY S. AND FINLAND, MAXWELL — *Archives of Internal Medicine*, 84: 857 (December) 1949.

The writers report the results of the clinical and laboratory studies made on 33 consecutive patients with pneumococcic pneumonia who were treated with aureomycin at the Boston City Hospital.

"Before any aureomycin was given these patients satisfied all the following criteria: (1) In each case the history and findings by physical examination were consistent with a diagnosis of pneumococcic pneumonia. Roentgenograms of the lungs were usually taken at the time of admission to the hospital, but occasionally they were taken a day or two later; these also showed lesions consistent with pneumococcic pneumonia in each instance. (2) All patients were acutely ill and febrile at the time the first dose of aureomycin was given. (3) No previous treatment with antiserums, sulfonamides or antibiotics had been given. (4) Blood and sputum were obtained for cultures, and pneumococci of specific types were isolated and identified from one or both of these sources."

"Each patient was observed closely and examined before and at frequent intervals after administration of aureomycin was started until they were well along in convalescence and the common laboratory tests were carried out as indicated. Roentgenograms of the lungs, in addition to those made on admission, were repeated as often as feasible, usually twice a week during the hospital stay."

"There was the usual predominance of males over females. The patients ranged

age from 13 to 75 years, with a predominance in the older age groups, and 8 the 33 patients, including 4 with bacremia, were 65 years of age or older."

"Sixteen different types of pneumococci re represented and two thirds of the ses were due to types 1 to 8, exclusive type 6. It is significant that in 6 of the maining 11 patients; that is, in the ones ving pneumococci of the so-called higher pes, the same type was obtained from th blood and sputum. A second type of eumococcus was identified in the sputum 2 patients in addition to type 2 pneucocci: type 7 in 1 and type 24 in the ner."

"Some significant underlying complicaon was present in 18 of the 33 patients. . Six of the patients had acute alcoholic oxication when admitted to the hospital; 3 of these patients delirium tremens veloped, either before or shortly after eatment with aureomycin was started, d 1 of the latter also had severe cirrhosis the liver. Evidence of chronic bronitis and bronchiectasis was made out om the history and the physical and entgenographic findings in 2 patients, d the patient with bronchial asthma had rsistent symptoms during the acute state the pneumonia and to a milder degree roughout the period of hospitalization. ne patient with rheumatic heart disease d signs of moderate pulmonary congeson and edema on admission to the hostal and was promptly digitalized. The undice noted in 2 patients was mild cterus index 12.5 to 20.0) and probably as related to the pneumonia, since it eared promptly after treatment was arted." The patient with agranulocytosis d diabetic acidosis and the 1 with the l cerebral injury both died.

"The sensitivity of the pneumococci obined from the blood and sputum was sted in 30 of the patients. All the strains the same type of pneumococcus obtained om the blood and sputum before treatent and from subsequent sputum samples nen pneumococci could still be isolated d the same sensitivity to aureomycin. ne sensitivity of the 32 different strains sted ranged from 0.39 to 3.12 micrograms r cc., the majority being completely inbited by less than 1 microgram per cc. . All but 5 of the 32 strains of pneumococci were at least as sensitive as Streptococcus 98, and 11 were two or four times as sensitive."

"The first dose of aureomycin was given in most instances on or before the fifth day of illness, and all the patients were acutely ill at the time. Pneumococcemia was demonstrated in the pretreatment blood cultures in one third of the patients. The pulmonary lesion, as judged by physical and roentgenographic indications, was limited to a single lobe in most of the patients; two or three lobes were involved in 9 patients, and in only 4 of the latter was the lesion bilateral.

"All the patients were febrile when aureomycin treatment was started, and the temperature at that time was below 101 F. in only 1 of them. In the majority, the temperature was 103 F. or higher, and in 3 patients it was over 105 F. The leukocyte counts ranged from 2,200 to 33,700 per cu. mm., with totals below 10,000 in 4 and over 25,000 in 6. An attempt was also made to arrive at a general estimate of the severity of the illness in each patient from all the observations made at the time aureomycin therapy was undertaken. Most of the patients were considered to be moderately or severely ill. In only 2 patients was the illness judged to be mild, and 1 patient was almost moribund at the time."

"Most of the patients received all the aureomycin by mouth in doses varying from 1.0 Gm. every four or six hours to 0.5 Gm. given at intervals of four, six or eight hours. In 9 of the 16 patients who received individual doses of 1.0 Gm., these were reduced to 0.5 Gm. after the temperature reached normal and the condition had improved.

"The total oral dose of aureomycin ranged from 5.5 to 46.5 Gm. given over a period ranging from 2 to 15 days. Most of the patients received less than 20 Gm. and were treated for five days or less. The average dose for the 27 patients who were treated orally was 17.7 Gm. given over an average of about five and one-half days.

"Parenteral therapy was used in the treatment of 6 patients. Two of these patients received repeated doses of 100 mg. each, some given intravenously and the rest intramuscularly at intervals of two to four

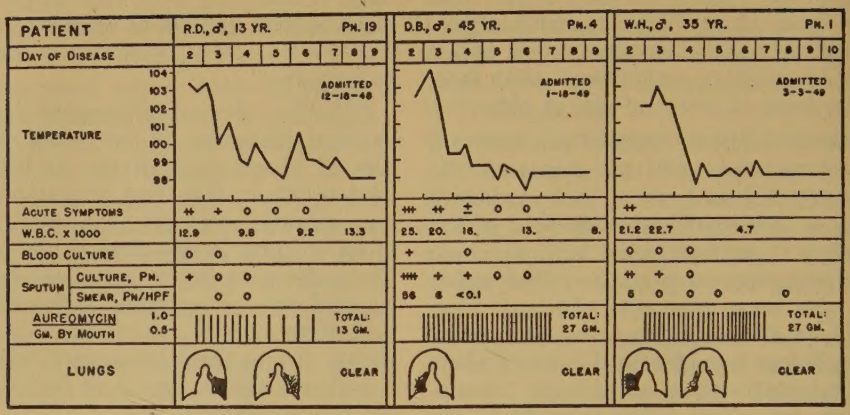


Chart 1.—Course and other significant data in cases of 3 patients with pneumococcic pneumonia treated with aureomycin by mouth.

hours. In these cases, each dose was given in 10 cc. of 0.7 per cent sodium carbonate solution, and the intravenous doses were given very slowly, 10 to 15 minutes being taken for each injection. Both of these patients died, 1 after receiving only five doses in 14 hours and the other after six doses had been given in 14 hours.

"Four other patients received aureomycin for their pneumonia only by the intravenous route. The individual doses for these 4 patients consisted of 500 mg. of crystalline aureomycin hydrochloride given in 1.0 or 1.5 liters of either isotonic sodium chloride solution or 5 per cent dextrose solution in distilled water. These were given once daily by slow drip, taking about an hour or longer for each injection. The initial dose for 1 patient was 750 mg. given in the same manner. No special buffers were used with these injections, and the reaction of the final solutions was about *p*H 3.5 to 4.0. The average total dose for these 4 patients was 2.05 Gm., and the interval between the first and the last dose averaged 72 hours.

"Two of the patients received penicillin in addition to aureomycin; 1 of them was the patient with agranulocytosis who died, and the other received the penicillin only during convalescence. No other antimicrobial agents were used for any of the remaining patients."

Chart 1 shows the course and other significant data in 3 cases of pneumococcic pneumonia of moderate severity treated with aureomycin by mouth.

Cuts similar to the one shown here which appeared in the original articles showed the following: data on 3 additional patients with pneumococcic pneumonia who were treated with aureomycin by mouth; data on 3 bacteremic patients over 65 years of age with pneumococcic pneumonia treated with aureomycin by mouth; course and data in 3 of 4 cases of pneumococcic pneumonia treated with aureomycin intravenously; course and data in the case of a patient with type 2 pneumococcus pneumonia treated with aureomycin by mouth and persistent fever and leukocytosis in the case of a patient with type 14 pneumococcus pneumonia treated with aureomycin by mouth.

Two of the patients 65 years old and bacteremic died within 18 hours of the time aureomycin treatment was started.

"There was a marked drop in temperature during the first two days after the administration of aureomycin was started in all 31 patients who recovered. In all but 6 of these patients the major reduction in the fever had occurred within the first 12 or 24 hours. There were only 8 patients in whom any fever persisted or recurred after the second day, and in these patients the temperature did not usually exceed 100 F. after that time. Three of these patients became afebrile during the third day, and in 2 others the temperature remained normal after the fourth day.

"Of the 3 patients whose fever persisted or longer than four days, 1 had delirium remens and in him a sterile pleural effuion also developed. . . . In a second patient he fever was associated with a persistent eukocytosis, but the patient had no localizng signs or symptoms of any complication nd the lesion in the lung was clearing apidly during this time. The fever subided while the aureomycin was still being iven, and test doses of aureomycin subequently failed to reproduce the fever; ience the fever cannot definitely be ascribd to the antibiotic. . . . In the third paient, the pneumonia began during a sere attack of influenza A, and treatment, hich was started with intramuscular oses, resulted in a slow but steady defer escence of fever, which cleared only after ral therapy was given."

"Improvement in the acute symptoms f the pneumonia usually paralleled the rop in temperature. In some patients the ubjective improvement actually preceded y several hours the major drop in temerature, and only an occasional patient ontinued to appear acutely ill for any ength of time after the temperature had ropped to a nearly normal level. There ere 5 patients who continued to have inor symptoms during the third and ourth day after treatment was begun but nly 3 continued to have significant symoms of acute illness after the fourth day."

"The lungs, in general, cleared rapidly fter aureomycin therapy was started. . . . Definite and usually marked clearing was vident from the physical signs and roentgen observations within six days after reatment was started in more than two hirds of the patients who recovered. Signs f consolidation or fluid persisted over ost of the affected area for more than ight days in only 3 patients.

"With the exception of these 3 patients, omplete clearing was demonstrated in entgenograms taken on or before the nd of the second week after the aureoycin treatment was initiated. In several atients, moreover, the last roentgenogram hich still showed pulmonary infiltrations be present had been taken from four to ight days earlier, and in most of them e pulmonary lesions had already largely eared at that time. The 3 patients whose sions persisted longer than two weeks were also the ones whose symptoms persisted the longest."

"Pneumococci were obtained from the pretreatment blood cultures in 11 patients, but only one of the blood cultures taken after treatment was started was positive. This culture was obtained nine hours after the first parenteral dose of aureomycin was given to the patient with agranulocytosis, and the next culture, taken three hours later, showed no growth."

"Attempts were made to identify and isolate pneumococci from the sputum in all of the patients before and at frequent intervals after aureomycin treatment was started. . . . In 11 patients, including 4 with bacteremia, the only specimens of sputum which yielded pneumococci were those obtained before the first dose of aureomycin. The first specimen in which pneumococci could not be identified either in direct smears or by the various cultural methods was obtained 8 to 12 hours after the first dose in 4 of these 11 patients, within the first 24 hours in 5 others and within 36 hours after treatment was begun in the remaining 2. There were only 2 patients in the entire series in whom pneumococci were still demonstrable in sputum more than 36 hours after treatment was started, the longest interval being 59 hours. It is thus seen that not only the pneumococcemia was promptly cleared but the pneumococci were rapidly eliminated from the sputum after the aureomycin treatment was started.

"Most of the strains of pneumococci isolated from sputum during or after the aureomycin treatment were tested for sensitivity to the antibiotic simultaneously with the corresponding pretreatment strains that had been isolated from both sputum and blood of the same patients. All strains of the same type obtained from the same patient were found to have identical sensitivity to aureomycin."

"In the 4 patients who were treated with daily intravenous injections, the effects on the acute disease and on the bacteriologic findings were quite similar to those observed in the patients who received larger and more frequent doses by mouth. The major drop in temperature and symptomatic improvement occurred in each of these patients before the second dose was

given. The optimum dose by the intravenous route has not been determined."

"The only significant untoward effects that resulted from oral aureomycin therapy were those referable to the gastrointestinal tract. Only 6 of these patients had nausea and vomiting; however, this was not sufficient to interfere with therapy, although the dose was reduced in some instances. Seven patients, including 5 of those who had some vomiting, passed large and bulky stools, usually two or four a day, which only occasionally became watery. In 19 patients there were no untoward effects from the oral preparations used."

"The intramuscular doses were accompanied with moderate pain that lasted for about half an hour, and there was residual local tenderness for several hours. In 1 of the 4 patients receiving the large intravenous doses there was extravasation of some of the solution of aureomycin at the time of the fourth injection and this resulted in some redness, tenderness and swelling along the course of the vein for several inches and later there was slight edema of the forearm. This all cleared in a few days.

"There were no instances of fever or rash and no evidence to toxic effects on the blood, kidneys, liver or nervous system attributable to either the orally or the parenterally administered aureomycin in any of the patients."

"Agglutination tests with antigens prepared from homologous and heterologous types of pneumococci were carried out in the acute and convalescent phase serums of 20 patients. Agglutinins for pneumococci of the homologous types were demonstrated in titers ranging from 1:2 to 1:16 in the convalescent phase serums of 11 of these patients, including 5 who had positive blood cultures. The other 10 patients in whose serums agglutinins could not be demonstrated included 3 who had pneumococcemia. However, the agglutination test, as used here, is not a very sensitive one for the demonstration of pneumococcus antibodies.

"Tests for cold agglutinins, Streptococcus MG agglutinins and anti-influenza A and B hemagglutinins were carried out in 26 of the patients. Cold agglutinins developed in low titer in 1 patient . . . . and were present in high titer in both acute and convalescent phase serums in another." The latter was the patient who had asthma. "No significant titers or rises in titer of agglutinins for Streptococcus MG were found in any of the patients." A significant rise in titer of antibodies for influenza A was demonstrated in 3 patients, including 1 in whom cold agglutinins also developed. The illness in these 3 patients occurred during the latter half of March 1949, when influenza A was prevalent in the community.

"The clinical and laboratory data which have been presented indicate that aureomycin hydrochloride given either by mouth or intravenously is highly effective in the treatment of pneumococcic pneumonia."

**Terramycin, a New Antibiotic** — Finlay, A. C., Hobby, G. L., P'an, S. Y., Regna, P. P., Routien, J. B., Seeley, D. B., Shull, G. M., Sobin, B. A., Solomons, I. A., Vinson, J. W. and Kane, J. H. — *Science*, 111: 85 (January 27) 1950.

"A new actinomycete, *Streptomyces rimosus,* has been isolated from a soil sample and so named because of the cracked appearance of the growth on the surface of an agar medium. When the organism was grown on plates containing nutrient agar and when a variety of bacteria including certain of the gram-negative enteric organisms, aerobic spore formers and gram-positive cocci were streaked across these plates, growth of the test organisms was inhibited in the vicinity of the colony of the actinomycete. When *Streptomyces rimosus* was grown under submerged aerobic conditions, the broth exhibited similar inhibitory powers, as demonstrated in serial dilution assays. From broth cultures of this organism, a crystalline antibiotic was isolated; the name Terramycin has been assigned to this compound.

"Terramycin is amphoteric and forms the crystalline hydrochloride and sodium salt. Crystalline Terramycin has the following properties: mp approximately 185° C with decomposition; $[\alpha]_D^{25}$ −196° (1.0 per cent in 0.1 *N* HCl). It is soluble in methanol, ethanol, acetone and propylene glycol, in water to the extent of 0.25 mg. per ml. at 25° C; insoluble in ether and

petroleum ether. Terramycin is stable over long periods in aqueous solutions at about pH 2.0-5.0, at room temperature. A sample of crystalline Terramycin analyzed: C, 53.05; H, 5.91; N, 5.64; O (by difference), 35.4.

"Terramycin crystallizes in several forms, depending upon the procedure used. One of these forms consists of thick hexagonal plates, the refractive indexes of which are $\alpha=1.636 \pm .004$, $\beta=1.644 \pm .004$, $\gamma>1.700$.

"In 0.1 M phosphate buffer (pH 4.5), Terramycin shows ultraviolet absorption maxima at approximately 247, 275, and 353 mμ. It also shows characteristic absorption in the infra-red region.

"The activity in vitro of crystalline Terramycin hydrochloride against a variety of microorganisms is shown in table 1. The activity was determined by dissolving varying amounts of the antibiotic in nutrient agar and streaking with the organisms under test. Further observations on the sensitivity of these and other organisms will be reported in detail elsewhere.

"Terramycin shows a low degree of toxicity in animals. The intravenous $LD_0$ for Terramycin hydrochloride is equivalent to 103 mg. of the crystalline amphoteric compound per Kg. of body weight in mice; the $LD_{50}$ is equivalent to 192 mg. per Kg.

Table 1
Activity in Vitro of Crystalline Terramycin Hydrochloride*

| Species | μg/ml. | Inhibition |
|---|---|---|
| *Aerobacter aerogenes* | 1.0 | 100% |
| *Klebsiella pneumoniae* | 3.0 | " |
| *Escherichia coli* | 5.0 | " |
| *Salmonella typhosa* | 3.0 | " |
| *S. paratyphi* | 1.0 | " |
| *S. schottmuelleri* | 1.0 | " |
| *S. pullorum* | 10.0 | " |
| *Shigella paradysenteriae* | 1.0 | " |
| *Bacillus subtilis* (FDA 219) | 3.0 | " |
| *Staphylococcus albus* | 1.0 | " |
| *S. aureus* | 1.0 | " |
| *Proteus* sp. | > 1000 | " |
| *Pseudomonas aeruginosa* | 100 | " |
| *Brucella bronchiseptica* | 3.0 | " |

* Activity is expressed in terms of the equivalent weight (μg) of crystalline Terramycin necessary to inhibit growth.

"As is the case with aureomycin and chloramphenicol, Terramycin is active in vivo as well as in vitro and displays marked chemotherapeutic activity against experimental infections in mice due to *Streptococcus hemolyticus, Diplococcus pneumoniae, Klebsiella pneumoniae, Salmonella typhosa,* and other organisms. It is effective by both the oral and parenteral routes of administration. Preliminary studies suggest that Terramycin has definite antirickettsial activity in the chick embryo. In high concentrations it appears to inhibit the infection of the chick embryo with the PR8 strain of influenza A virus."

**The Most Important Clinical Aspects of Boeck's Sarcoidosis** — ALVES MEIRA, JOÃO—*Anais paulistas de medicina e cirurgia,* 58: 291 (October) 1949.

After a historical survey the author points out that the affection under consideration has been described under various terms, including Boeck's sarcoid or benign lupoid, Besnier's lupus pernio, Mortimer's disease, Tennesson's disease, benign lymphogranulomatosis, Boeck - Schaumann's disease, Besnier-Boeck-Schaumann's disease, and sarcoidosis.

The disease is not as rare as formerly assumed and more than 1,000 cases have been reported; it has been recognized more frequently since systematic chest roentgenograms have been taken and since more attention has been paid to its multiple localizations. The disease shows a global distribution. In Switzerland about 1.5 million soldiers were examined systematically and the disease was suspected in 115 and confirmed in 67 of them. Any age may be involved, but the highest incidence is found during the fourth decade of life. Females are more frequently involved. In the United States Negroes are more frequently involved, even where the colored population is not very large. Familial occurrence has been observed.

Histologically the sarcoid lesion represents a so-called firm or solid tubercle which is formed by a mixture of large pale epitheloid cells and a relatively large but variable number of typical Langhans' giant cells with some lymphocytes and plasmocytes. Neutrophils and eosinophils are usually lacking or present in small numbers.

The cells may show vacuoles and particularly the giant cells may show inclusions of variable shape, described as asteroid or radial or inclusions with a double contour, or lacunar inclusions; their significance is unknown and they are not specific, but have not been found in association with definite lesions of human tuberculosis. Radial or asteroid inclusions have been encountered in leprosy, torulosis, and foreign body granulomas. Double contoured or laminated inclusions seem to consist of concentric deposits of an amorphous material impregnated with variable amounts of calcium and iron salts around a nucleus of some foreign material, like rests of elastic fibers; they have also been encountered in lesions caused by beryllium. The hard tubercle is characterized by lack of caseification, but a small central area of necrosis may exist. In pure cases the search for alcohol acid-fast bacilli is negative. The macroscopic size is usually that of a grain of corn; the number is variable. Where numerous tubercles are present they are located around small blood vessels or lymphatics and substitute for the normal tissue structure involved as in spleen and lymph glands. There is no tendency to confluence, but a false impression of fusion is sometimes created, as shown by special staining methods. The histologic aspect of sarcoid lesions may persist unchanged for long periods of time or absorption may take place. Fibrosis and hyalinization may result, leading to an acellular fibrous nodule. Around the tubercles the fibrous tissue may show infiltration with lymphocytes and some plasmocytes. Any part of the organism may be involved, in variable combinations, but there is a predilection for lymphoid tissue. The clinical syndrome will depend on localization. Sarcoidosis is a chronic affection of long duration, with periods of complete spontaneous regression and of exacerbations. Reabsorption in some areas may be concomitant with development of new localizations. There is discordance between clinical symptoms and extent and degree of the lesions. Extensive pulmonary lesions may be found roentgenologically in cases without clinical symptoms on the part of the lungs. The systemic symptoms vary in intensity and may include weakness, anorexia, articular pain, low fever, and symptoms caused by mechanical effects of the lesions. The systemic symptoms usually disappear during the chronic, stabilized or regressive phases. The peripheral as well as intrathoracic and intra-abdominal lymph glands are almost always involved; they are usually small, firm, painless, mobile and free, without tendency to fusion or suppuration. Only a few lymph glands may be involved and they rarely reach a large size. Biopsy may show the characteristic lesions even when the lymph glands are only discretely enlarged. Bilateral hilar adenopathy is frequently visualized roentgenologically. Contrary to carcinomatous metastases and lymphomas there usually are no signs of obstruction. Pulmonary atelectasis if present is due to bronchial lesions rather than obstruction by the lymph glands, as demonstrated by bronchoscopic biopsies. Involvement of the abdominal lymph glands is usually recognized only on laparotomy. The tonsils have been found involved more frequently by European than by American authors, probably because of the high incidence of tonsillectomy in America. Marked splenomegaly may be caused by splenic localizations. In the author's case the spleen extended to the left iliac fossa and near the midline, and was firm, regular, painless, and showed normal notches; on tests of splenic contraction it behaved like a slightly congestive spleen.

Among 29 autopsied cases splenic lesions were found in 21. The liver is less frequently involved. Liver function tests are normal as the lesions involve chiefly the periportal spaces, sparing large parenchymatous areas. Puncture biopsy of the liver may be diagnostic. The lungs are frequently involved; pulmonary symptoms may include cough, expectoration, slight fever, and small hemoptyses, with a relatively satisfactory general condition. The author's case was not seen until two and a half years after onset and the chest roentgenogram was similar to that of hematogenous miliary tuberculosis; particularly the lower lobes are involved and the nodules may be larger than those of miliary tuberculosis. Over a period of a year repeated roentgenograms showed no change in the author's case. A reticular form with linear areas or fascicles extending from the hili along the bronchovascular markings are less frequent and resemble the picture of

nphangitic carcinomatous metastases or silicosis. More rarely the roentgenogram ows an area of fibrotic induration or eas of massive condensation, suggestive an infiltrative pneumonic process. Pulnary lesions are usually accompanied hilar adenopathies. The sarcoid lesions disseminated in the interstitial lung sue, suggesting hematogenous propagan of the etiologic agent with predilecn for areas near vessels, interlobar nphatics, and subpleural areas. The lens may regress completely. Destructive itary lesions may occur, without demonable acid-fast bacilli during life or on opsy. This is important as in 10 per t of the autopsied cases a combination sarcoidosis and tuberculosis has been nd. The pulmonary lesions may occur hout cutaneous ones, and the diagnosis st be made by exclusion of tuberculosis, efly by ganglionary biopsy. A cardiac alization leads chiefly to alterations of rhythm, like transitory or permanent ck without other electrocardiographic erations; the heart may be enlarged and gestive heart failure may result. In e cases of unexplained tachycardia diac sarcoidosis may be suspected. spnea and cyanosis may be caused by diac localization of the process or by ensive pulmonary fibrosis with or with- endarteritis, with the picture of a onic cor pulmonale. Cardiac lesions e been found in 20 per cent of autopsied ons and sudden death is frequent. Renal ons have been found in 20 per cent of opsied cases and may lead to albumia, azotemia, and poor kidney function. blood pressure is usually normal. eous lesions occur in 15 to 25 per cent he cases with other lesions but their incidence is unknown; the short bones tarsus, carpus and vertebrae are inved with preference. Only the bone row may be involved and such lesions escape roentgenologic diagnosis. The acteristic osseous lesion of sarcoidosis termed cystoid multiple osteitis and tgenologically presents either the pic- of the circumscribed form with cytoid s of medullary rarefaction without reonal component or that of a diffuse with multiple areas of rarefaction of ticular aspect. Both types may coexist he same case. The osseous lesions may be associated with external manifestations like fusiform deformations of the fingers and ankles, subcutaneous periarticular nodules, and dystrophic alterations of the nails. As generally the periosteum is not involved and the joints remain free; these deformations are painless. Leprosy may be simulated by these lesions.

Older reports assume an incidence of 40 to 50 per cent of cutaneous lesions in sarcoidosis, but with better recognition of cases with visceral manifestations this incidence tends to become lower. There are three main aspects of cutaneous lesions; namely, Boeck's sarcoid, the sarcoid of Darier-Roussy, and Besnier's lupus pernio. The first most frequently involves infiltrative plaques of the entire thickness of the skin, of oval shape and variable size, with a purple or dark red color, and chief localization at the level of extensor surfaces of the upper limbs, back and face. Nodules, papules and small tumors may also be encountered and are firm and elastic, showing the same distribution. An annular or circinate aspect may be present. The second form is composed of more deeply located hypodermic nodules, often with symmetric localization, at the extensor surfaces of the limbs and the trunk. The third form is constituted by erythematous infiltrated thick red or blue plaques located at nose, ears, face, cheeks, and limbs. Schaumann described a type with plane erythrodermic plaques; erythema nodosum may be the initial manifestation of sarcoidosis.

The mucous membranes are involved in 10 to 20 per cent of cases. Obstructive phenomena are produced in the nasal mucosa and hoarseness and stenosis may be produced in the larynx. Pharynx, trachea, bronchi, eyes, and lacrimal and salivary glands may also be involved. Uveitis, iritis, or iridocyclitis, unilateral or bilateral in character, may be the first manifestation. Synechiae, corneal opacities, and glaucoma with loss of vision may result or regression may take place. Choroiditis, retinitis retinal perivascularitis and involvement of the optic nerve may occur, sometimes associated with cerebral lesions and diabetes insipidus. Uveitis with bilateral involvement of the parotid and sometimes the submaxillary glands constitutes Heerfordt's syndrome or uveoparotid fever; facial paralysis occurs rather frequently

in this syndrome. Sarcoidosis of the lacrimal and salivary glands produces Mikulicz's syndrome.

Involvement of the central nervous system has been demonstrated both clinically and anatomically. The peripheral nerves are only exceptionally involved; this is important for differential diagnosis from leprosy. Granulomas in the hypothalamic and pituitary region may cause diabetes insipidus. Testicles, prostate and thyroid gland may be involved while contrary to tuberculosis the suprarenals are only exceptionally involved. A gastrointestinal localization is exceptional. Some authors attribute some cases of regional enteritis to sarcoidosis. Pancreatic, muscular and serosal localizations have no clinical significance.

Hematologic alterations are not characteristic and vary with the localization of the process. Leukopenia may occur; monocytosis occurs during active stages in relation to activity of the reticuloendothelial system, and eosinophilia may occur. Anemia is usually discrete, and secondary polycythemia occurs in extensive pulmonary fibrosis. Hypersplenism with leukopenia, anemia and thrombocytopenia may occur in cases with splenomegaly. Cases of thrombocytopenic purpura are on record. The sedimentation rate may be increased during active stages. The most important chemical blood finding is hyperglobulinemia, with inversion of the albumin-globulin ratio, and responsible for the hyperproteinemia. The gamma fraction of the globulins is involved in the increase, due to impairment of the reticuloendothelial system according to some authors. Hypercalcemia has been encountered, without relation to osseous involvement and to the blood phosphorus level but related to an increase of the nonprotein nitrogen. The phosphorus level may show slight elevation and the same applies to the alkaline phosphatase; the cholesterol level may be reduced. The urea and nonprotein nitrogen level is increased only in renal involvement, but some authors consider an extrarenal azotemia as well.

Anergia or hypergia to tuberculin is important and occurs in 60 to 70 per cent of cases. Recently Kveim's intracutaneous reaction has been used for diagnosis of sarcoidosis; it seems to be specific but requires a long observation period for its interpretation. The antigen is prepared from glandular or cutaneous sarcoid tissue and its intracutaneous injection provokes formation of a papule with the histologic characteristics of sarcoidosis. The papule may appear late and may persist for months.

The diagnosis of sarcoidosis is difficult. In the author's case tuberculosis, Hodgkin's disease, brucellosis, diseases of the hematopoietic system with splenomegaly and splenomegalies of other origin had to be considered. Generally lymph gland biopsy will clarify the diagnosis. Examination of the tonsils, and liver puncture biopsy may be helpful. Sarcoidosis has a benign highly chronic course. Pulmonary tuberculosis is the most frequent complication. Fatal hemoptysis has been reported.

Many authors consider sarcoidosis as atypical tuberculosis; supervening tuberculosis manifests itself by transformation of tuberculin anergy into tuberculin allergy and the lesions become caseous and contain acid-fast bacilli. According to others sarcoidosis represents a tissue reaction to many different microorganisms and also to dead agents, and therefore as systemic reticuloendotheliopathy of a granulomatous infectious-allergic character. Anticutins have been assumed as cause of the tuberculin anergy by the advocates of a tuberculous etiology. A tuberculous etiology cannot be definitely ruled out but has not been proved either. A relationship to leprosy has also been claimed, and various other infectious origins have been mentioned. Attention has been called to the possible role of phospholipids in the formation of epithelioid cells. Generally speaking the etiology of sarcoidosis must still be considered as unknown.

The treatment is purely empirical. Results of treatment with arsenicals, bismuth, gold salts, chaulmoogra oil, x-rays, radium, ultraviolet rays and other methods have not been so satisfactory. Spontaneous remissions make evaluation of any treatment difficult. Recently vitamin D (calciferol) in high doses, 50,000 to 300,000 daily, has been recommended; careful observation is indicated with this treatment in order to avoid possible toxic effects.

**Erythema Multiforme Exudativum (the Stevens-Johnson Syndrome)** — DRESNER, ELLIS — *Lancet*, 2: 1036 (December 3) 1949.

A case of severe erythema multiforme exudativum (Hebra) is presented. It is of interest because of the extraordinary severity followed by complete recovery, and the negative results of bacteriological investigations.

"A butcher's assistant, aged 27, was admitted to hospital on May 22, 1948. Fifteen days before admission he developed a sore throat with fever and sweating. He stayed in bed for three days, and during that time took 7 Gm. of sulphadiazine prescribed by his doctor. On the fourth day he returned to work feeling improved. Six days later he developed small 'blisters' on the lips, tongue, and mouth, with malaise, frontal headache, and anorexia. During the next 24 hours purplish spots developed on the face, forearms, hands, and feet, and spread to the neck, shoulders, and thighs, and some became vesicular. The mouth was then very painful, and two days after the onset of the rash the patient complained of painful swelling of the right elbow. During the day before admission he became increasingly prostrated, with generalised abdominal discomfort, nausea and retching, and difficulty in swallowing. There was a dry cough, and the left knee and ankle became swollen and painful. Micturition was unaffected, and the bowels were slightly loose.

"On the day before admission a small nephew sleeping in the same room was admitted to an infectious diseases hospital with mild scarlatina, and three days later his brother-in-law, also living in the same house, developed a 'septic sore throat'; but no bacteriological investigations were made.

"Past History.—Apart from measles in infancy there had been no previous illness. By reason of his occupation the patient had been liable to minor sepsis of the hands and fingers, and had had an infection of the right fourth finger about four weeks previously, which healed in a few days without specific treatment.

"On examination the patient was a slim pale young man, desperately ill and prostrate. Temperature 98.4° F., pulse rate 128, respirations 20 per minute. He had well marked foetor oris and a recently healed paronychia on the right fourth digit. Scattered over his face, neck, shoulders, arms, and legs were circular purplish red circumscribed vesicles surrounded by a narrow zone of erythema. They were mainly on the extensor surfaces of the arms and the flexor surfaces of the legs, and were especially numerous on the buttocks. The trunk was clear, apart from two lesions in the right groin and on the scrotum. The vesicles varied from a few millimetres to more than a centimetre in diameter, the larger ones lying over bony prominences, such as the elbows, metacarpophalangeal joints, and malleoli. They were not umbilicated and contained a thin sanguineous fluid. On the mucosa of the lips, palate, mouth, and pharynx were numerous cherry red macules on which were superimposed small vesicles. Many were eroded. The lips were fissured and bleeding, the tongue was coated, and there was a purulent gingivitis. The pharynx and tonsils were injected, and the tonsillar glands were enlarged and tender. There was no other lymphadenopathy, and nothing abnormal was found on examination of the cardiovascular, respiratory, and central nervous systems. The blood pressure was 125/95 mm. Hg. The ocular fundi were normal. The abdomen was soft, and the liver and spleen were impalpable. Effusions were present in the left knee and ankle joints; and, though there was no swelling of the right elbow, movements there were restricted and painful. The other joints were normal.

"Investigations.—The urine contained much protein but was otherwise normal. A blood count showed red cells 6,000,000 per c.mm., Hb 118 per cent (Sahli), white cells 21,600 per c.mm. (neutrophils 72 per cent, lymphocytes 14 per cent, monocytes 14 per cent). The bleeding time and clotting time were normal. Capillary fragility was not increased (Hess test negative). Radiography of the chest was normal.

"Treatment and Progress.—Parenteral penicillin was given from the day of admission and was continued for 35 days. Soluble sulphathiazole was also given intramuscularly from the second day, but was discontinued when streptomycin therapy was begun. No new skin lesions appear-

ed, but some of the vesicles became pustular. All the oropharyngeal lesions became eroded, and small sloughs formed on them. Despite dysphagia the patient took fluids by mouth, and these were supplemented by saline solution given per rectum. Dysuria was complained of during the first week, but there was no urethral discharge.

"May 25: Streptomycin therapy was begun with a dosage of 0.5 Gm. four hourly. The skin lesions were drying, but oral sloughs were spreading and becoming confluent, and there was profuse salivation. The mouth gave rise to considerable anxiety in spite of constant attention. Joint effusions were unchanged.

"May 28: The patient's condition had deteriorated. His temperature was 101° F., with increased prostration and trismus. His mouth and throat now presented an alarming picture, since the entire buccal mucosa, palate, and fauces were concealed by a thick greyish white adherent membrane, and there was constant oozing of blood from the fissured lips. Next day this false membrane began to separate, leaving a raw bleeding surface, and the patient complained of severe burning retrosternal pain on swallowing. The joint effusions were resolving. Streptomycin was discontinued, a total of 6.5 Gm. having been given. During the next four days the temperature continued elevated and irregular, with a disproportionately high pulse rate. Large sloughs separated from the mouth, gums, and pharynx, with slight loss of tissue, and the retrosternal pain continued. Large doses of nicotinamide, riboflavin, and ascorbic acid were administered.

"May 31: Neoarsphenamine 0.15 Gm. was given intravenously on alternate days. The patient had now developed rales at both lung bases and a loose cough with increasing amounts of watery sputum. Small amounts of fresh blood and melaena, with traces of mucous and necrotic tissue, were passed per rectum, and his haemoglobin level had fallen.

"June 2: A transfusion of fresh blood was given, after which there was no more bleeding per rectum, but at this stage haemorrhages and exudates were first noted in both ocular fundi.

"June 6: All cutaneous lesions had crusted and fallen off, and the condition of the mouth had much improved. The patient was taking solids by mouth but still salivated copiously, and the amount of sputum was about 20 ounces daily.

"June 11: There was definite consolidation of the right lower lobe. Separation of sloughs from the mouth was now complete, leaving the oral mucosa friable and hyperaemic. Sulphathiazole was given by mouth in gradually reduced doses for the next 10 days, by which time the consolidation had resolved.

"June 13: The patient was afebrile, in spite of a severe laryngitis lasting five days early in convalescence.

"July 22: He was discharged, the only residua of the illness being deeply pigmented coppery spots at the sites of the larger skin lesions, and loss of the uvula, which had sloughed completely. These pigmented spots were still present when he was seen six months later, and some had central depressions covered by fine scars but he was otherwise well and free from symptoms.

"Laboratory Investigations.—The highest white cell count after admission was 21,000 per c.mm. on June 1 (polymorphs 89 per cent, eosinophils 1 per cent, lymphocytes 7 per cent, monocytes 3 per cent); the eosinophils never rose above 2 per cent. The heavy albuminuria noted on admission persisted until the patient was afebrile. Occasional red and white cells were noted a few times. The urine was sterile throughout.

"Repeated attempts at culturing organisms from the blood, vesicle fluid, throat, and an excised skin lesion were negative or grew only contaminants. During the stage of pulmonary consolidation *Str. pneumoniae* and a penicillin-resistant *Staph. aureus* were found in the sputum. The blood Wassermann and Kahn reactions were negative, as also were serum agglutinations against the typhoid, paratyphoid, abortus, and salmonella groups, and the Paul-Bunnell and Weil-Felix reactions. The Strauss reaction and complement fixation and conglutination tests for *Pf. mallei* were negative, and injection of vesicle fluid into a guinea pig gave negative results. The blood antistreptolysin titre was 60 units per ml. at the height of the illness.

"Virus neutralisation tests against herpes virus were done on the serum on 2 occa-

ons: at the middle of the illness and early convalescence. On both occasions there as a positive titre at 1/16, which was onsidered not significant.

"Histological examination of an excised utaneous vesicle showed a nonspecific in-ammation, and no organisms or inclusion odies were seen.

"Electrocardiograms: On June 9 the T ave was flat in all limb leads and chest ads; on the seventeenth the T wave was ill isoelectric in leads II and III; and on une 30, the T wave was upright in all ads and of normal voltage."

**ularemia. Report of a Case Treated Successively with Streptomycin and Aureomycin** — CARROLL, HUBERT H. AND GORMAN, JOHN E.—*United States Naval Medical Bulletin*, 49: 1085 (November-December) 1949.

"Recently the authors observed the re-lts of the use of streptomycin and Aureo-ycin successively in 1 case of human laremia of the ulceroglandular type."

"The patient, a 62 year old white female . . . was admitted to the hospital on pril 25, 1949. She had become ill with vere chills, fever, and general malaise April 9, 1949 and two days later two istules appeared on the index finger on e right hand. Since then chills and fever d been present daily, and she had noted e progressive enlargement of the lymph des in the right epitrochlear area and the ght axilla. She was treated during this me with penicillin and sulfadiazine with noticeable improvement.

"Further questioning revealed that dur-g the weeks preceding her illness both e patient and her son had repeatedly ndled wild rabbits brought home by their t dog. Her son had become ill with an entical illness, including infection of the gers, at the same time as the patient."

"The patient was an elderly white male who appeared acutely ill. There ere two ulcerative lesions about 1 cm. diameter on the right index finger and ere was moderate tenderness and en-rgement of both the epitrochlear and ght axillary lymph nodes. The heart and ngs were normal to examination, and e liver and spleen were not palpable. oentgenogram of the chest was normal.

"Agglutination tests of the patient's serum for *Pasteurella tularensis* were negative at the time of admission, but because of the typical clinical picture of the disease, treatment was started at once with streptomycin in daily doses of 1.5 Gm. However, the patient continued to have extreme general malaise and a daily temperature elevation to approximately 100° F. During the following 10 days there was no subjective or objective improvement in the patient's condition, although she received continuous streptomycin therapy. The dose of the drug was increased twice until she was receiving 3 Gm. daily during the final days of this period. On the evening of May 4 Aureomycin therapy was started in dosage of 500 mg. every four hours; streptomycin was discontinued. The following day the patient voluntarily stated that she felt much stronger and that her general malaise and weakness had noticeably decreased. On the morning of May 6 the temperature became normal and remained normal during the following seven days of Aureomycin therapy. There was improvement in the tenderness and swelling of the lymph nodes although moderate swelling did remain at the time of the patient's discharge from the hospital.

"The diagnosis of tularemia was confirmed by a persistent rise in the agglutination tests of the patient's serum for *Past. tularensis*. One week after admission this agglutination was read at a strength of 1:640. The patient was discharged on May 16 in excellent general condition. The only residual sign of her disease at that time was moderate enlargement of the lymph nodes in the right epitrochlear and right axillary area."

"This case is unusual in view of the poor response to streptomycin in spite of adequate dosage. In most of the previous case reports streptomycin in a dose of 1 Gm. daily usually caused the temperature to return to normal limits within 48 hours. Cases with a longer duration of fever were those in which the disease had been present for two weeks or longer before treatment was started. However, even in these cases improvement usually occurred within four or five days. In the case reported here, even after 10 days of therapy with

streptomycin, the patient's condition showed slight clinical improvement and her temperature had not decreased from that at the time of admission. Following the use of Aureomycin the patient noted a prompt improvement in her general condition and commented upon it without questioning. This was substantiated objectively by the return of temperature to normal limits and decrease in tenderness and size in the involved lymph nodes. It is possible that this prompt response to Aureomycin was aided by the fact that virulence of the infective organism was attenuated by the preceding streptomycin."

**Auscultation. A New Conception of the Respiratory Murmur and Its Place in Diagnosis** — POTTENGER, F. M. — *American Review of Tuberculosis*, 60: 639 (November) 1949.

The writer wishes to show that the respiratory murmur is composed of sound vibrations which originate in all component parts of the respiratory mechanism, and to point out how this fact may be used advantageously in the physical examination of the lungs.

"For more than a century auscultation has been accepted as the chief measure on which dependence can be placed in the physical diagnosis of diseases of the lungs and pleura; and yet, as taught, it is not satisfactory."

"It is evident to anyone who will examine carefully that, normally, inspiration is not longer than expiration—10:2, 5:3, 3:1, etc., as taught; but actually shorter.

"The weakness of the respiratory murmur in case of abdominal breathing indicates that the air column passing through the larynx and bronchi and expanding the air cells cannot be the origin of the respiratory sounds, for the air enters the air passages the same as it does in the usual type of breathing, yet the murmur is weak." One also has a respiratory murmur when the larynx is by-passed by the bronchoscope.

"Moreover, it is not rational to accept without questioning that the murmur heard near the hilum and in the interscapular region is produced, even chiefly, by the air as it passes the glottis, enters and dilates the bronchi, impinging on their surfaces, and that in the main portion of the lung, by air entering and dilating air cells."

Relation of Respiratory Murmur to Respiratory Mechanism.—"After noting that inspiration is not longer than expiration, the writer was next impressed with the fact that there is a muscular element in the murmur. By placing the stethoscope over a contracting biceps, a sound was heard which possessed some of the qualities of the respiratory murmur. It was noted during normal breathing that a fairly good but weak murmur could be heard over the abdominal muscles. A murmur was also noted over the chest wall where the lungs were collapsed by pneumothorax and the lung tissue was separated widely from the chest wall by an air cushion. Such murmurs are usually weak if the pressure is marked, but sometimes, when the parietal pleura is thickened, they may not be far from normal in their intensity, indicating that different factors enter into their production. The thickness of the pleura alters the murmur, sometimes increasing and sometimes decreasing it. More recently a weak respiratory murmur was heard over the chest wall where the lung had been removed by pneumonectomy. Surely the entry of air could not be responsible for this sound because the pulmonary elements with the air current had been removed from the side.

"To what can the sounds be attributed in pneumothorax and pneumonectomy, where a little air may enter in the one case, and none in the other? On careful analysis the answer seems evident. The respiratory murmur begins with the inspiratory movement and ends with the adjustment of the pulmonary tissues at the end of the expiratory movement. Is it not reasonable then to attribute the murmur to the respiratory mechanism every part that causes and transmits sound vibrations; the muscles, the bony cage, the pleura when inflamed or thickened, the mediastinum especially when pathological, the bronchi, the pulmonary tissue, the air passages, and the column of air?"

"That part of the respiratory mechanism which is responsible for the bronchial murmur is normally limited to the superior portion of the chest and is most distinct posteriorly. Here the sound vibrations are produced by the air current, the larger

onchi, a comparatively small amount of lmonary tissue, a heavy musculature, d the least elastic portion of the bony ge.

"On the other hand, that part of the spiratory mechanism which is largely re- onsible for the vesicular murmur is minant in the anterolateral and lower rtions of the lungs. Here the murmur composed of vibrations which originate structures largely air containing (the er bronchi and air cells) plus a limited usculature and an elastic bony cage."

In auscultation of the normal lung and eura, one is listening to the complex und caused by vibrations in the respira- ry mechanism in action, and in patholog- al conditions, one hears that modification the normal sounds which the particular thological process causes in the action the respiratory mechanism.

In the sounds heard on auscultation it evident that there are two distinct fac- rs which must be taken into considera- n: sound production and sound trans- ission. "Sometimes one is predominant, d again, the other. The respiratory mur- ur heard at any given point consists of composite sound originating in that por- n of the respiratory mechanism which is nsmitted to the ear at the point of ob- rvation.

"Infiltrations in the lung alter respira- ry movement and, according to their ture, size, density and location, change e sounds. They act in two ways:

"First, acute inflammatory processes ch as active tuberculosis cause spasm of ical muscles, particularly the sterno- idomastoid, scaleni, levator anguli apulae and acromial portion of the apezius above, and the crus and central ndon of the diaphragm below, and mod- y respiration by reflexly lessening the vement of the hemithorax in which the thological process is located.

"Second, all infiltrations, whether in- mmatory or noninflammatory, interfere th full respiratory movement by their esence, the amount of interference vary- g with the extent and character of the filtration. They also modify sound trans- ission.

"It readily can be seen that the effect both the reflex and the infiltration per is to slow and lessen both the inspiratory and expiratory movement. This alters the sound vibrations. It prolongs both phases of the respiratory murmur and in many instances produces a higher pitched note. If the infiltration results in much fibrosis, then the murmur may show the above disturbances to a high degree and be transmitted with increased force." This one sees in the increased voice transmission caused by extensive scar tissue in tuberculosis, particularly when situated near the apex; or in a cavity with smooth walls surrounded by dense scar tissue—the pectoriloquy of Laennec.

"The respiratory murmur may have different qualities according to the individual chest, the part of the chest in which the infiltration is located, and the particular characteristics of the infiltration. All of these factors will influence respiratory movement differently. One rarely finds a markedly harsh murmur or marked voice transmission when the infiltration is small, scattered, or situated deep in the lung, surrounded on all sides by functioning pulmonary tissue, no matter what the characteristics of the pathologic process. If the infiltration is small, the respiratory mechanism may be influenced so little that the presence of the pathology may be wholly overlooked on auscultation."

Emphysema, such as one finds in chronic bronchitis, bronchiectasis, asthma, or the compensatory emphysema found in chronic, far advanced tuberculosis, changes the respiratory movement and the accompanying murmur according to the following pattern which varies according to the degree of emphysema present: The lungs at rest are dilated; the intercostal spaces are distended; the bony cage is fixed and rigid; and the diaphragm is depressed and incapable of full movement. "Every factor which enters into normal respiratory movement is limited in its activity, hence the respiratory murmur is weak.

"In pneumothorax, the auscultatory sounds consist partly of the weak contraction of the chest muscles and those made by the feeble movements of the bony cage, plus whatever pulmonary tissue there is to engage in the respiratory movement. In pneumonectomy the stretching of the tissues which occupy the former lung space in response to respiratory effort may produce detectable sound vibrations.

"In a chronically contracted lung the pulmonary, the muscular, and the bony cage elements of the respiratory murmur may or may not be largely removed and the sounds vary accordingly. But if there is marked fibrosis or a cavity in the midst of dense scar and the air freely enters, the vocal sounds may be strongly transmitted. This is bronchophony and pectoriloquy, in which transmission greatly overshadows sound production.

"Diseases of the pleura may also alter the respiratory movement and change the respiratory murmur. Acute pleuritis causes local spasm of the intercostal muscles and reduces the movement of that segment of the bony cage over the part of the pleura which is inflamed, causing a decrease in the intensity of the murmur. It also may cause a friction rub when the inflamed surfaces move on each other. Should an effusion occur, the nature of the sounds will depend on the amount of fluid present. Much fluid distends the intercostal spaces, reduces the movement of the muscles and bony cage, separates the pulmonary tissue from the parietal pleura, and lessens the respiratory sounds.

"Rales and the Respiratory Mechanism.—Rales may be heard in pathological conditions of both the lungs and pleura. They are called crepitant, subcrepitant, gurgling, and musical. Roughly speaking, the first three varieties are considered to be caused by mucus in the bronchi, air cells, and cavities, while the musical rale is an obstructive rale caused by partial blocking of a bronchus. But there are pleural rales which cannot be distinguished from nonmusical rales of pulmonary origin.

"The writer knows of no sure way to differentiate the fine and moderately coarse rales originating in the lung from those originating in the pleura. Both may be heard on deep inspiration and on expiration followed by cough and a quick inspiration; and both may now and then be heard on both inspiration and expiration.

"The best evidence for differentiating these rales depends on the pulmonary and pleural reflexes; and this is not wholly satisfactory.

"If atrophy of the subcutaneous tissue is present and does not extend below the second rib anteriorly and the spine of the scapula posteriorly, rales heard are most likely of pulmonary origin, because this is the area of the pulmonary trophic reflex.

"If atrophy is found anywhere between the second rib anteriorly and the spine of the scapula posteriorly above, and the lower margin of the ribs, this shows that the pleura has been inflamed and as a result the intercostal and subcutaneous tissues are degenerated and rales heard over these areas are likely to be of pleural origin. The fact that sometimes rales are not heard does not mean that no pathology is present.

"When the trophic reflex extends from the apex down below the second rib anteriorly and the spine of the scapula posteriorly, rales are uncertain as to origin, for this indicates that both pulmonary and pleural tissues have been involved.

"After inflammation of the pleura has subsided, or an effusion has become absorbed, the overlying intercostal and subcutaneous tissues may be permanently degenerated and alteration of the respiratory movement and murmur may persist. Degeneration of the subcutaneous and intercostal tissues with alteration of the murmur frequently follows the thickening of the parietal pleura caused by the irritation of the air in case of pneumothorax treatment. In some of these cases, rales are found and occasionally pain is present. Detectable atrophy is nearly always present if the pneumothorax has been maintained for more than a few months.

"Rales arising in both the pulmonary tissues and the pleura may be persistent, and pleural rales may be permanent."

"It is not at all uncommon for the movement of the chest wall, hence the respiratory murmur, to be perceptibly lessened if the previous pleural involvement was extensive.

"Pain may recur years after the acute phase of the pleurisy has passed, especially under conditions of low energy, tiring, emotional stress, worry and disappointment, menstruation, and changes in weather."

Constructive Suggestions.—"This discussion takes away much of the independent value heretofore ascribed to auscultation and shows that all methods of physical examination of the lungs and pleura are interdependent. It raises auscultation from

its dependence on the erroneous belief that the respiratory murmur is caused by the rush of air into the bronchi and air cells, and gives as its basis vibrations arising in the respiratory mechanism.

"With this new conception the so-called vesicular murmur is heard in the anterosuperior, lateral, and lower portion of the lung, where the pulmonary tissues are dominant in the production of sound vibrations; and the so-called bronchial murmur, in the hilar area and the posterosuperior portion, where the nonpulmonary tissues are dominant, as has long been taught. Infiltrations, no matter where located, reduce the dominance of the vibrations from the pulmonary tissues and make the sounds take on what Laennec called a bronchial quality.

"The terms bronchial and vesicular may be retained but they should be assigned to the entire respiratory mechanism and carry the new meaning of dominance in nonair-containing tissues in the production and transmission of the bronchial murmur, and dominance in the air-containing tissues in the vesicular murmur.

"By carefully inspecting and palpating chests, the examiner may determine with fair definiteness how the respiratory mechanism is disturbed. He should pay due regard to the reflex spasms and degenerations caused by pathological changes in both lungs and pleura, and also note the effect on both the form and movement of the chest caused by infiltration and other pathological changes. Prominent among these are emphysema, rigid thorax, and marked contraction, which are often evident to the eye and more fully determined by palpation and percussion. If he will make these initial observations he will have some idea of what the respiratory murmur may be before putting a stethoscope on the chest. However, he must not expect to find the same sounds caused by the same pathology in all chests." One has been taught to expect to find far greater changes in the murmur than are present, especially where infiltrations are small or widely scattered. "It is surprising to find how often they are so slight as to be almost unrecognizable.

"The examiner must make more of physical examination of the chest than the use of auscultation and percussion. It must mean a complete and careful study of the patient's respiratory mechanism. Seeing and feeling are of equal importance to hearing. Disturbed physiology, as shown in the reflexes and in interference with the respiratory mechanism, which may be determined by inspection and palpation, take on added importance and must be utilized in order to obtain a full picture of any disease affecting either the lungs or pleura. Physical examination must be rewritten with due emphasis on the utilization of all data obtained on sight, touch, and hearing, rather than limiting it to what is heard through the stethoscope and determined by the use of the percussing finger."

**The Antitreponemal Effect of Oral Chloromycetin in 32 Cases of Early Syphilis in Man. A Preliminary Report**—ROMANSKY, MONROE J., OLANSKY, SIDNEY, TAGGART, S. ROSS AND ROBIN, EUGENE D.—*Science*, 110: 639 (December 9) 1949.

Since the use of chloromycetin in the treatment of gonorrhea has been reported and since it seemed to have some antitreponemal activity in rabbit syphilis, the writers decided to study its effect upon the Treponema of human syphilis.

"Patients with lesions containing numerous *Treponema pallidum* were selected for this study. The first 4 cases received 120 mg./Kg. of chloromycetin per day. Two of these received an additional priming dose of 4 Gm. The next 4 patients received 60 mg./Kg./day, and the remaining 24 received 30 mg./Kg./day. Except in a few instances the antibiotic was administered orally in six equal doses at 4 hour intervals." Seven patients could not be followed up.

"Treponema were not found in the lesions of the first 4 cases 22 to 26 hours after treatment was started. The treponemal disappearance time in the next 4 patients was 23 hours. Two cases given 30 mg./Kg./day were negative in dark field microscopic examination in 26 hours.

"Since there was rapid disappearance of the Treponemas from the local lesions on a relatively large dose it was decided to investigate the minimal effective dose of the antibiotic. A single oral dose of 250 mg. was given to 3 cases, the lesions re-

mained positive for Treponema in dark field examination even at 48 hours. Two cases were given 500 mg. in a single oral dose; the lesions in 1 became negative in dark field examination in 48 hours, and the other remained positive even at 96 hours. In these cases treatment was subsequently instituted on a 30 mg./Kg./day schedule for 6 days with complete healing of the lesions.

"In order to determine whether the treponemal disappearance time could be decreased, 1 case was given 2 Gm. every 4 hours for six doses, a second case 2.5 Gm. every 4 hours for six doses, and a third case 12 Gm. as a single dose; the treponemal disappearance time was 24, 26, and 24 hours, respectively. Apparently increasing the dose of chloromycetin does not appreciably shorten the treponemal disappearance time.

"These findings suggested that an oral chloromycetin dosage of 30 mg./Kg./day divided into six doses and given at 4 hour intervals might be effective in the treatment of early syphilis. Therefore, a total of 24 patients were treated with 30 mg./Kg./day for 4, 6, or 8 days. The lesions in all cases showed evidence of initial healing within 24 hours and most of them showed complete healing by the end of therapy. Some delay in healing occurred in a few cases where the location of the lesion predisposed to a slower response. For example, a patient with a urethral chancre took 6 days to heal because of the constant flow of urine over the lesion."

Chloromycetin seems to promote healing by a different mechanism from penicillin. "Penicillin produces initial healing at the periphery of a lesion, whereas healing with chloromycetin therapy seems to be initiated from the base of the lesion. This is particularly striking in the large ulcers of benign late syphilis of the skin.

"Quantitative serologic tests using the Eagle flocculation test for syphilis were performed prior to therapy and at monthly intervals after treatment." There was a rapid decline in serologic titer in most cases at the end of one month following treatment.

"Two of the patients who received 30 mg./Kg./day were pregnant. The clinical and serological response until now has been satisfactory in both patients. One patient has delivered a live child. Although serologically positive at birth, clinical and serologic progress in this child have been excellent without further therapy. The second patient is still pregnant.

"The only toxic or untoward reactions noticed with the dosages of chloromycetin utilized in this study were an occasional mild diarrhea and an occasional complaint of dryness of the mouth. The Jarisch-Herxheimer reaction in chloromycetin-treated patients is either less frequent than that observed in penicillin-treated cases or of such a mild nature that it is frequently missed. Only 2 patients were observed to have very mild reactions 48 hours after treatment was started. Several patients complained of a generalized aching sensation 48 hours after treatment began, but no fever or eruptions were noted. As these symptoms disappeared in 8 to 12 hours, despite further therapy, they may have been Jarisch-Herxheimer reactions.

"Since relatively small doses of chloromycetin will cure acute gonorrhea, attention should be called to the possible danger of masking the diagnosis of syphilis.

"Studies with the use of chloromycetin for the treatment of syphilis are continuing, and are being extended to include the late manifestations of syphilis. One patient with late syphilis manifested by extensive gummas of the leg is now under therapy with chloromycetin. This patient has had a dramatic healing response within four days after treatment was started."

**Risks of Antihistamine Medication** — *Lancet*, 1: 28 (January 7) 1950.

"The introduction and development of antihistamine drugs in the last dozen years has been a notable advance in therapeutics, and their success in allergic diseases has naturally led to their trial in ailments on or beyond the borders of the allergic group. Since they have been particularly valuable in paroxysmal rhinorrhoea, it was inevitable that they should be tried in the common cold." In medicine, one is told, sensible experimentation is preferable to speculation, so such trials were obviously desirable. "The aetiologies of the two conditions are generally agreed to be quite different—the one allergic and the other a virus in-

fection—but it was argued that the symptoms of the early coryzal and congestive phases of a cold might be allergic in origin and that at this stage an antihistamine drug might abort the cold before secondary infection had occurred. Individual practitioners who have experimented on themselves seem to agree that the antihistamines afford some symptomatic relief, and Brewster's trial in the United States Navy was encouraging so far as it went, though the plan was subject to serious criticism. On the other hand, Paton, Fulton, and Andrewes, who emphasized the difficulty of assessing 'cold cures,' reported a small but carefully controlled experiment to test the value of 'Anthisan' and concluded that the results did not show any dramatic effect of this drug on the common cold. They added this rider concerning their findings:

"'We do not bring them forward as evidence that there is no beneficial action, but only to draw attention to the necessity for rigorous control of any test of a remedy for colds; the need to depend on subjective judgments by patients and clinician alike make such tests particularly difficult.'

"A cautious attitude on the part of doctors is highly desirable, if only because the Poisons Board has not, so far, taken steps to prevent the public from buying these toxic drugs over the counter. It is said that by the Monday evening after an article had appeared in a Sunday newspaper on the virtues of antihistamines as a cold cure, stocks of them in the chemists' shops were almost exhausted. It seems likely that of the thousands of people who bought these drugs at least a third would experience some toxic effect, such as drowsiness, giddiness, or the peculiar psychological states of unreality and disorientation. Trivial as this may appear, there will certainly be tragic consequences if drivers of cars and public transport dose themselves indiscriminately with antihistamines. The decision not to include these drugs in the Poisons Schedules was doubtless made at a time when it could reasonably be assumed that the people taking them would normally be under immediate medical supervision. Today this applies only to a minority, and the change of circumstances has created a potential danger which merits immediate intervention by the Ministry of Health. The possibility that a labyrinthitis may develop on withdrawal of antihistamine therapy, of which 3 examples are reported by Cherry for South Australia, also deserves consideration."

According to reports several children have died from eating sugar-coated antihistamine tablets as sweets. "In cases of acute poisoning by antihistamines the obvious antidote is histamine acid phosphate, injected subcutaneously in doses of 0.1 mg. per Kg. of body weight." Tablets which are vividly coloured and sweet to taste can scarcely be resisted by a normal child, and one has the unfortunate experience with ferrous sulphate tablets as evidence of this fact. "Responsibility for safe disposal of poisons in the household rests with its adult members; but manufacturers might consider whether the time has not come to incorporate into the coating of these tablets a trace of some bitter substance which would discourage a child without causing undue hardship to adults."

**A New Sulfonamide (Gantrisin). Studies on Solubility, Absorption and Excretion** — SVEC, FLOYD A., RHOADS, PAUL S. AND ROHR, JOSEPH H. with the Assistance of Ida Kraus—*Archives of Internal Medicine*, 85: 83 (January) 1950.

A new compound, 3,4-dimethyl-5-sulfanilamido-isoxazole (Gantrisin), appears to show considerable promise as an effective sulfonamide.

"The toxic manifestations encountered have been similar in nature to those produced with other sulfonamides with the exception of the absence of renal complications." The writers have used the drug in the treatment of 300 patients, without any evidence of renal damage, even though alkali therapy was seldom used. "In order more fully to evaluate the merits of Gantrisin, studies were made on solubility, absorption and excretion. The compound was supplied in the oral tablet form and as a 40 per cent solution of the ethanolamine or diethanolamine salt for intravenous and intramuscular administration."

"The solubility of Gantrisin rapidly increases from 60 mg. per 100 cc. at *p*H 5.4

to 327 mg. per 100 cc. at *p*H 6.14, whereas the solubility of sulfadiazine at *p*H 6.3 is only 12.9 mg. per 100 cc. The solubility of sulfadiazine approaches that of Gantrisin only after the *p*H of the urine is raised to 7.5 or 8. The free form of Gantrisin is more soluble than the acetylated form up to *p*H 6.6, whereas the opposite is true of sulfadiazine. About 70 per cent of the excreted Gantrisin is in the free form, which is the most soluble fraction."

"Oral and intramuscular administration was in 1 or 1.5 Gm. doses every four hours, day and night. In a few instances 2 Gm. was given every four hours. When the drug was given intravenously, the dosage was usually 2 Gm. every eight hours. It was injected directly into the vein in a period of one to two minutes in some cases. In others, it was given slowly in 1 liter of 5 per cent glucose solution or in isotonic saline solution. Up to 12 Gm. per day has been given in some instances without any untoward effect.

"Ten patients received intramuscular injections of the 40 per cent solution of the ethanolamine salt of Gantrisin, 1 Gm. every four hours for two to three days, and 2 patients received a 40 per cent solution of the diethanolamine salt of Gantrisin in a similar manner. Twelve patients received a similar amount of the 40 per cent solution of ethanolamine salt intravenously in fluids, and 7 patients were given the 40 per cent solution of diethanolamine salt. Single initial doses up to 4 Gm. occasionally were given directly into the vein when a quick high level was desired, as in the treatment of bacterial meningitis. No untoward reactions were noted from the intramuscular or intravenous use of Gantrisin."

"Blood levels produced by a uniform dosage of Gantrisin (1 Gm. every four hours orally, intravenously or intramuscularly) were determined, as well as 24 hour urinary excretions. The amount of the drug that was conjugated was determined by subtracting the concentration of the free form from that of the total."

"The highest blood levels, averaging 11.7 mg. per 100 cc. of the free form and 16.7 mg. per 100 cc. total, were obtained when the drug was given intravenously. The next highest levels, 6.61 mg. per 100 cc. free and 9.29 mg. per 100 cc. total, were obtained when it was given intramuscularly. The lowest levels, 5.85 mg. per 100 cc. free and 9.17 mg. per 100 cc. total, were obtained with oral administration.

"The acetylated portion varied between 28 and 35 per cent and was about the same in the urine as in the blood. The route of administration had very little effect on the degree of acetylation. The average total amount of the drug excreted during a 24 hour period was likewise similar for all three methods of administration, varying between 3.61 and 4.12 Gm. on an intake of 6 Gm., with an average of 3.85 Gm. excreted in 24 hours. Assuming that 1,500 cc. of urine was excreted during a 24 hour period, this represents a urinary concentration of 257 mg. per 100 cc.

"Since the solubility of Gantrisin is such that a concentration of 265 mg. per 100 cc. is present in normal urine at *p*H 6.06, it would appear that there would be relatively little danger of crystalluria at *p*H 6, whereas sulfadiazine does not approach this solubility until the *p*H of the urine is above 7.6."

The levels of Gantrisin in the spinal fluid were found to be about one-third those in simultaneously drawn blood samples.

"To follow more closely the absorption and excretion of Gantrisin, patients were given a single 2 Gm. dose by various routes. Frequent blood samples were drawn for the determination of blood levels, and the sulfonamide excreted during a 48 hour period was measured."

"The highest blood levels, 16 mg. per 100 cc. in 30 minutes, were obtained when the drug was given intravenously. The concentration in the blood rapidly decreased, and 8 mg. per 100 cc. was left two hours after injection. The total 48 hour urinary excretion was 88 per cent of the original dose, 33 per cent being excreted during the first eight hours. When the drug was administered intramuscularly, a peak blood level of 8 mg. per 100 cc. was reached at six hours and 88.2 per cent of the administered dose was excreted in the urine in 24 hours. Blood levels of 9 mg. per 100 cc. were reached two to three hours after the oral administration of a single 2 Gm. dose, 94.3 per cent of the dose being excreted in 48 hours. The most

rapid excretion occurred during the first eight hours.

"It is appreciated that there is considerable variation in the rate of absorption among various persons when the drug is given orally or intramuscularly."

"The studies on excretion indicated that there is no appreciable retention of the drug provided the renal function is adequate. About 70 per cent of the excreted drug is in the free form, and the other 30 per cent is in the conjugated form."

**Granulocytopenia and Thrombocytopenia from Streptomycin Treatment** —Oppenheim, Marc and de Meyer, Gonzague — *Schweizerische medizinische Wochenschrift*, 79: 1187 (December 10) 1949.

On the basis of numerous experiments on monkeys, dogs, guinea pigs, rats and mice one came to the conclusion that streptomycin has no effect on the blood. Only exceptionally an appreciable hematologic damage could be produced with streptomycin; namely, macrocytic anemia with neutropenia in white rats, which could be cured with folic acid; this suggests that peroral streptomycin administration may make the physiologic intestinal flora incapable of synthetizing folic acid. Conditions concerning allergic or toxic side effects of streptomycin on the blood are similar in human pathology, and in their most extensive monograph to date several writers state in 1948 that anemia, leukopenia or thrombocytopenia was not produced in any of their cases by streptomycin. Since then exceptional cases of side effects on leukopoiesis, thrombocytopoiesis or erythropoiesis, or on several of them combined, have been reported. Eosinophilia has been observed most frequently and seems prognostically of no importance; it has been encountered in 13.5 to 75 per cent of the cases. A monocytosis was reported of 10 to 20 per cent, approximately simultaneous and parallel to the eosinophilia. The Council on Pharmacy and Chemistry reported 930 cases with 5 observations of moderate leukopenia and relative neutropenia, and 3 cases of agranulocytosis. Anemia and hemorrhagic syndromes have also been reported. One writer collected 10 cases of combined damage to all three hematopoietic systems.

The authors' own case concerned a woman, aged 30, with a negative family and personal history, who developed increasing fatigue, cough, mucous expectoration, anorexia, amenorrhea, constipation and fever. Examination on admission three and a half months after onset revealed fever of 38.5° C., hepatosplenomegaly, a shift to the left in the white blood picture with 21.5 per cent staff cells and a total of 7,400 leukocytes, and positive urobilinogen and Ehrlich's reaction in the urine; the chest plate showed a soft infiltration the size of a cherry in the right basal region and a dense fine miliary propagation in both lungs. The eyegrounds showed numerous recent choroid tubercles, particularly on the left side. The spinal fluid was negative. A diagnosis of miliary tuberculosis, late primary infection with early generalization, was made. No tubercle bacilli could be found in sputum, gastric juice, feces, urine or spinal fluid at any time; animal inoculations with spinal fluid, urine, and gastric juice were negative, and the Mantoux reaction was negative in dilutions of 1:1,000,000 and 1:100,000.

Streptomycin treatment was instituted on the day after admission, starting with 1.5 Gm. daily; subsequently the dosage was increased to 2.0 Gm., and later it was reduced to 1.0 and finally to 0.5 Gm. Nine days after starting the treatment a generalized rash consisting of fine maculas appeared. From the nineteenth day on, 5 to 7 Gm. of paraamino salicylic acid was given daily in addition to the streptomycin, later being reduced to 2 Gm. On the twenty-fourth day of treatment granulocytopenia and thrombocytopenia supervened; the leukocytes numbered 700, there were almost no platelets, the hemoglobin was 68 per cent, and the erythrocytes numbered 3.23 million. There was epistaxis and the Rumpel-Leede symptoms were positive after one minute. Treatment was discontinued and blood transfusions and penicillin treatment were instituted. The leukocytes recovered rapidly, rising to 14,000 within 6 days, while the thrombocytes increased only to 48,000 within 12 days. After an interval of nine days streptomycin treatment was started again cautiously and with a lower

dosage but again the number of leukocytes and thrombocytes decreased, a number of hemorrhagic symptoms appeared, and the bleeding time rose to more than 30 minutes. After another larger series of transfusions the thrombocytes and leukocytes increased slowly so that after six weeks dihydrostreptomycin treatment in a dosage of 1.0 Gm. daily could be started. With this treatment the thrombocytes rapidly rose to normal and at times even above normal values while leukocytes and erythrocytes, after having reached normal levels, again slowly fell three weeks later; therefore dihydrostreptomycin was discontinued after 7 weeks and only resumed after an interval of 24 days when the leukocytes and erythrocytes had reached normal levels. The hemoglobin remained stationary between 80 and 85 per cent, and the absolute number of lymphocytes remained nearly normal throughout the entire period of treatment. The eosinophils reached a first relative maximum of 25 per cent four weeks after admission when the leukocytes numbered 700, and a second one of 8 per cent 4 weeks later when the leukocytes numbered 6,900; both times the thrombocytopoiesis was at its minimum. The total dose was 48.5 Gm. of streptomycin and 58.5 Gm. of dihydrostreptomycin.

This course seems to prove that a direct toxic effect of the streptomycin itself was dealt with and not an effect of the miliary tuberculosis or the paraamino salicylic acid, or its combination with the streptomycin. The thrombocytopoiesis particularly showed definite sensitization to the streptomycin, while dihydrostreptomycin seemed free of side effects on thrombocytopoiesis and seemed to have only very slight effects on leukopoiesis and erythropoiesis. The tuberculosis took its course rather independent of the at times dramatic hematopoietic phenomena. The patient was definitely afebrile 15 weeks after admission, and the choroidal tubercles were healed or on the way to healing. Over a period of three weeks peritoneal symptoms were present, perhaps to be interpreted as focal reactions, and treated with green soap inunctions. One month later the hitherto progressive or at least stationary pulmonary roentgenologic findings began to show signs of regression, both with respect to the primary focus and the miliary propagation. After the discontinuation of the dihydrostreptomycin treatment for 24 days the margins of the left papilla were still slightly blurred and a new large choroid tubercle appeared in the periphery on the same side. Lung function tests showed considerable emphysema with increase of the dead space and its ventilation; the patient was able to increase her respiration to such an extent that her blood was fully arterialized at rest. The general condition improved considerably; the patient gained weight and was able to be up. There were no meningitic symptoms at any time. At times the urine showed some albumin, and frequently urobilin and rarely urobilinogen. The blood pressure was always low and the sedimentation rate always more or less increased. Amenorrhea was persistent. The patient was transferred to a sanatorium; the prognosis seems doubtful.

**Aureomycin in the Treatment of Infectious Mononucleosis** — LYONS, HAROLD A. — *United States Naval Medical Bulletin*, 49: 1076 (November-December) 1949.

The writer reports 3 cases of infectious mononucleosis treated with aureomycin.

"Case 1.—K. E. C., a 26 year old white male, was admitted on February 12, 1949 with a history of general malaise, fever, pain in legs, back, and joints for four days. Vomiting had occurred once. There was no abdominal pain, diarrhea, or cough, but he had a slight sore throat. Physical examination: temperature, 102° F.; pulse, 96; respirations, 20; blood pressure, 140/70; ears, slight reddening of both canals; there was no nuchal rigidity. A few transient dry rales which disappeared on coughing were present in the right posterior field of the lungs. The remainder of the physical and neurological examination was normal. Laboratory report: red blood cells, 4.5 million; white blood cells, 3,000 per cu. mm. (on admission).

"On the first hospital day his temperature was 102° F., and the patient was quite lethargic. The white blood cell count on this day was 2,900 per cu. mm. with 4 per cent band forms, 40 per cent polymorphonuclears, 52 per cent lymphocytes (40 per cent of which were atypical), 2 per cent monocytes, and 2 unidentified

cells. General supportive measures were prescribed and 200,000 units of penicillin were administered three times a day.

"On February 14, 1949 a blood smear showed 50 to 60 per cent mononuclear and lymphocytic cells characteristic of infectious mononucleosis. Two grams of aureomycin a day were then administered. The spleen was not palpable nor were there any enlarged lymph nodes. On February 15 the sternal marrow aspiration smear was normal; the temperature was 100° F. On February 17 the leukopenia persisted; the BSP showed 40 per cent retention in 45 minutes; the thymol turbidity was 1.98 units; urinalysis was negative; chest roentgenogram was normal; and urine urobilinogen was negative. On February 20 the aureomycin was discontinued. The temperature was normal from the second day of therapy and the patient felt well. On February 21 the heterophile agglutination was negative; cephalin flocculation was 2 plus in 24 hours and 3 plus in 48 hours; white blood cell count was 8,500 per cu. mm. with a differential count of 44 per cent segmented granulocytes, 52 per cent lymphocytes, 2 per cent eosinophils, and 2 per cent monocytes; the sedimentation rate was 2.0 mm./hr.; and the thymol turbidity was 3.33 units. On February 23 the zinc turbidity was 6.8 units. On March 3 the heterophile agglutination was again reported negative.

"The patient felt well and was up and about the ward the first day his temperature was normal. His temperature remained normal from the seventh hospital day and the first day of aureomycin therapy. The liver and spleen were never palpable. There was no lymphadenopathy, and the pharynx was normal. He was discharged to duty March 9, 1949.

"Case 2.—E. A. S., a 23 year old male, was admitted on February 26, 1949 with a history of general malaise, stiff neck, headache, and constipation of six days' duration. Two days before admission he noted malaise, fever, and chills. The past history was noncontributory.

"Physical examination: Temperature, 101° F.; pulse, 90; respirations, 18; and blood pressure, 120/70. The pharynx was red; there was no nuchal rigidity; the posterior cervical lymph nodes were enlarged but not tender. Laboratory report: Red blood cell count, 4.47 million; white blood cell count, 10,600 per cu. mm., with a differential of 30 per cent segmented neutrophils, 66 per cent lymphocytes with many immature and Downey type mononuclear cells; the heterophile agglutination was positive in a dilution of 1:224.

"On the second hospital day when the temperature was 102° F., 2 Gm. aureomycin a day were administered. Within 24 hours the temperature was normal, the pharynx had cleared, the cervical adenopathy was no longer present, and the patient felt well. He was ambulatory on the fourth hospital day, and was discharged to duty on the seventh day.

"Further laboratory work revealed that the heterophil was still positive in 1:224 dilution on the sixth hospital day. His white blood count was 9,000 per cu. mm. with a differential of 22 per cent segmented neutrophils, 78 per cent lymphocytes including atypical vacuolated mononuclear cells; the blood Kahn reaction was negative; the serum zinc turbidity was 12.4 units; the serum phenol turbidity was 13.7 units; and the urinalysis was negative.

"Case 3.—W. H. M., a young adult male, was admitted on March 5, 1949, complaining of chills, fever, and malaise. Twenty-four hours before admission he had a moderately severe chill during the night. He then noted myalgia, fever, and a sore throat. Anorexia, myalgia, and malaise became progressively worse.

"Physical examination: Temperature, 102° F.; pulse, 100; respirations, 20; and blood pressure, 120/80. The pharynx was red and covered with an exudate. Cervical lymph nodes were palpable; the neck movements were guarded; the liver edge was palpable and tender; the spleen was thought to be palpable; and the axillary and epitrochlear lymph nodes were enlarged and palpable.

"Red blood cell count, 3.9 million; hemoglobin, 13.0 Gm.; white blood cell count, 11,650 per cu. mm., differential count, 32 per cent segmented neutrophils, 45 per cent nonsegmented neutrophils, 22 per cent lymphocytes, and 1 per cent atypical mononuclear cells; the sedimentation rate was 15 mm./hr.; and urinalyses and blood Kahn reactions were negative.

"On March 7, 1949, the fourth hospital day, the white blood cell count was 6,500

per cu. mm. with a differential of 43 per cent segmented neutrophils, 54 per cent atypical mononuclear cells (Downey type), and 3 per cent eosinophils; the heterophile agglutination was positive in 1:56 titer; zinc and phenol turbidity of the serum were normal; and the total proteins, serum albumin, and serum globulin were normal.

"On March 9, the second hospital day and the sixth day of the disease, 2 Gm. aureomycin were administered. The next morning his temperature was normal and he was symptomless. The drug was discontinued after 24 hours and at this time the liver was not palpable. The posterior cervical lymph nodes gradually receded and disappeared on the ninth hospital day. On March 21, the sixteenth hospital day, the white cell count was 7,300 with a differential of 32 per cent lymphocytes, 3 per cent monocytes, and 63 per cent segmented neutrophils, and 2 per cent nonsegmented neutrophils.

"He was discharged to duty on the twentieth hospital day, but was ambulatory after the fifth hospital day."

**Infectious Mononucleosis. Report of a Relapsing Case Treated with Chloromycetin** — HIRSCH, FREDERIC G. — *United States Naval Medical Bulletin*, 49: 1081 (November-December) 1949.

The writer reports the results of Chloromycetin therapy in a case of protracted, relapsing infectious mononucleosis.

"Case Report.—A 42 year old naval officer, who had been in good health until late July 1948, developed general malaise associated with pain in the cervical region. The malaise became more severe during the first week of the illness, and at its conclusion, cervical and inguinal lymphadenitis was demonstrable. During the second week dysphagia developed, and physical signs of a posterior pharyngitis were present. Fever did not exceed 100° F.

"Physical examination revealed a well developed, slightly obese, pyknic type of individual. The skin was clear. The posterior pharynx was reddened and slightly edematous mucosa and generalized nontender lymphadenopathy was noted. The spleen was not palpable but on percussion the area of splenic dulness appeared to be increased. On pressure in the left flank, some tenderness was elicited. From time to time during the course of the disease, a twisting motion of the trunk to the left produced pain in the left flank. Otherwise, the physical examination was negative.

"Roentgenogram of the chest showed only a healed childhood type of complex in the hilar region.

"Examination of the peripheral blood showed: hemoglobin, 14.0 Gm.; white blood cells, 9,000; differential: polymorphonuclears, 45; immature polymorphonuclears, 6; lymphocytes, 32; monocytes (mostly atypical), 16; eosinophils, 2; and basophils, 0. The large percentage of typical 'mononucleosis cells,' the relative lymphocytosis, the lymphadenopathy, and the symptoms were sufficient to warrant a diagnosis of infectious mononucleosis.

"At that time a heterophile antibody titer was 1:28. The test was repeated many times since then, but no higher titers have been found. Usually they were around 1:8.

"At weekly intervals between August 1948 and March 1949 peripheral blood films were examined. Between 10 and 16 per cent of large mononuclear cells typical of the disease were present. On no occasion during this period was any difficulty encountered in demonstrating these cells in the smears.

"During this same period the patient felt distinctly below normal. Malaise would frequently recur for several days followed by periods of improvement. He complained of easy fatigability and recurrent pain in the cervical, inguinal, and flank regions; fever was not prominent. The adenopathy persisted and seemed exaggerated when the subjective symptoms became worse. The spleen was never palpable.

"Treatment was symptomatic; usually coal tar analgesics or aspirin were prescribed. Adrenal cortical extract . . . . was administered for several weeks with improvement in the subjective symptoms, but without apparent effect on the lymphadenopathy, or on the peripheral blood picture."

In March, Chloromycetin was administered in the form of 250 mg. capsules according to the following schedule: For the initial dose, 50 mg./Kg. of body weight was given in three divided doses. "Thereafter 0.5 Gm. was given at four hour

intervals for the next eight days. A total of 25 Gm. was administered.

"Prior to treatment with Chloromycetin physical examination was made and found essentially negative, except for the presence of a generalized, shotty lymphadenopathy. The spleen was not palpable.

"The hemogram showed essentially the same picture that had been present for the previous seven months: hemoglobin, 12.5 Gm.; white blood cell count, 9,400; polymorphonuclears, 56; immature polymorphonuclears, 5; lymphocytes, 22; monocytes, 12; eosinophils, 3; and basophils, 2.

"There were many easily recognized large mononuclear cells of the lymphocytic series. The nuclei demonstrated fenestration, were deeply lobulated, and, in some instances, bizarre. The cytoplasm stained deeply and presented a 'foamy' appearance. Frequent cytoplasmic vacuoles were found.

"A recheck on the heterophile antibody titer was 1:8. Agglutination studies for brucella and tularensis antibody titers were negative.

"Liver function was normal as indicated by an icterus index of 4; a negative cephalin flocculation test; and a thymol turbidity of 2.9 units.

"During the first 48 hours of Chloromycetin therapy there was an apparent exacerbation of all signs and symptoms. The lymphadenopathy seemed exaggerated, and the subjective symptoms became more profound. . . . The number of atypical lymphocytes increased significantly.

"After this exacerbation the symptoms abated and the adenopathy gradually subsided until, at the end of two weeks, no nodes were palpable except for one in the left supraclavicular region. The hemogram became normal. It was apparent to both the patient and to the author that something had occurred coincident with the administration of Chloromycetin which radically altered what had been a relatively static clinical picture for seven months.

"The most striking feature in the hemogram was the disappearance of the typical 'mononucleosis cells' from the peripheral blood, and that the remaining monocytes appeared normal. If the presence of these cells in the peripheral blood can be regarded as evidence of the continuing activity of the disease, then, coincident with the administration of Chloromycetin, the disease became inactive.

"Side Effects: During the period of administration, the patient stated that his sense of taste was altered; food lost its savor, and smoking was not pleasant. The other side effect was the dramatic appearance of a sensitivity response. Shortly after the evening meal on the sixth day of treatment, and about two hours following the ingestion of 0.5 Gm. of the drug, the patient suddenly felt somewhat dizzy; his face became flushed; numerous red macular lesions about 0.5 cm. in diameter appeared over the face; and the pulse and respiratory rates became accelerated. There was no associated pruritus. These signs and symptoms persisted for about 30 minutes, and then subsided spontaneously. The same syndrome recurred shortly after the last dose of the course of treatment.

"Course: Since the completion of Chloromycetin therapy the patient has had no recurrence of signs or symptoms other than the complaint of occasional fleeting pains in various parts of the body. These can be largely accounted for on a psychosomatic basis. There is no residual adenopathy except for the persistent node previously mentioned, and the peripheral blood picture appears entirely normal."

**Therapeutic Action of Streptomycin and Promizole in Clinical Ocular Tuberculosis. A Preliminary Report** — Woods, Alan C.—*Archives of Ophthalmology*, 42: 521 (November) 1949.

"In the application of any form of supposedly specific therapy to ocular tuberculosis, one is always beset with the uncertain nature of the diagnosis. In the absence of tissue for biopsy and material for animal inoculation or from which the bacilli may be isolated, the diagnosis must perforce be presumptive. Therefore, in the evaluation of any new form of therapy, the diagnostic criteria should be unusually rigid.

"There were two guiding principles in the choice of patients to be treated. The first principle was that the diagnosis of ocular tuberculosis in any treated patient must be so firm that it would meet the approval of an experienced ophthalmologist. The diagnostic criteria observed were

as follows: (*a*) The ocular disease must conform to a pattern commonly regarded as tuberculous, and one in which histologic examination of eyes with similar disease patterns had uniformly demonstrated the probable tuberculous nature of the disease; (*b*) the patient must show elsewhere in the body evidences of a preceding tuberculous infection, a source from which the ocular infection might logically have arisen; (*c*) the cutaneous reactions to tuberculin must be in conformity with those for the patient's age and tuberculous status, and (*d*) the most thorough and exhaustive medical survey possible should reveal no other systemic disease or cause to which the ocular inflammation could logically be attributed. . . . The second guiding principle in the selection of patients was that the ocular disease either had not yielded to more conventional forms of therapy or did not appear amenable to such therapy and that the condition of the patient was sufficiently desperate to warrant any risk that this treatment might entail."

Thirteen of the writer's 14 patients met these criteria.

"The 14 patients treated with streptomycin and Promizole may be grouped as follows: Three had generalized uveitis, 1 with concomitant scleritis; 4 had classic sclerokeratitis, all with anterior scleritis and pronounced corneal involvement; 1 had diffuse scleritis, both anterior and posterior, with proptosis and limitation of movement of the eye; 4 had severe exudative choroiditis, all with some involvement of the anterior ocular segment with mutton fat keratic deposits and Koeppe nodules, and 2 had hemorrhagic retinitis, or Eales's disease."

"In the evaluation of results, it must be remembered that each observation of a therapeutic response is entirely uncontrolled."

"To the first patient treated, streptomycin was first given alone, and Promizole was added only two weeks before cessation of the streptomycin therapy. This patient was treated before the synergistic action of the two agents had been demonstrated, and therapy was planned with the idea that the Promizole would be continued after a full course of treatment with streptomycin (120 Gm.). To the second patient, Promizole alone was given for a period of seven months, and streptomycin was added only when the patient had an exacerbation. To all other patients, streptomycin and Promizole were given synchronously, and the combination was continued until what was considered a 'full course' had been given or the occurrence of toxic symptoms indicated that one or the other agent should be withdrawn.

"The total proper doses of streptomycin and Promizole for ocular tuberculosis are still undetermined both in experimental animals and in man. On the basis of the information gleaned from experimental observations, and the published clinical reports on the amounts of streptomycin used in treatment of systemic human tuberculosis, it was first decided that a 'full course' of streptomycin for ocular tuberculosis in man would be equivalent to a dose somewhere between 120 and 200 Gm. Inasmuch as definite clinical improvement was noticed after the administration of much smaller amounts, and one was naturally fearful of vestibular damage with the prolonged use of streptomycin, it was decided to cut the total dose of streptomycin first to 65 Gm. and later to 42 Gm. if these amounts could be taken without toxic symptoms. Certainly, satisfactory immediate clinical results were obtained with as little as 26 Gm. of streptomycin combined with 156 Gm. of Promizole, but whether or not these results will be permanent, or whether the patient will later show recurrences, remains to be seen. For the present . . . . it would appear that when streptomycin is given with Promizole a total dose of 42 Gm. of streptomycin given in doses of 0.5 Gm. twice daily would be sufficient in all but especially severe and resistant cases. As far as Promizole is concerned, the drug is relatively nontoxic in doses of 6 Gm. a day. When toxic symptoms appear, they are quite definite—fever, vertigo, anorexia, malaise, leukopenia and dermatitis—and they disappear immediately on withdrawal of the drug. Therefore if the drug is being well tolerated, and there appears to be any clinical indication for its further use, there is little reason that it should not be continued after the course of streptomycin is completed." However, in the writer's cases a total of 250 Gm. appeared adequate, al-

though many patients took far greater amounts. A red color of the urine is the rule in Promizole-treated patients and should not be considered a toxic reaction.

"Therapeutic Response.—In all of the 14 cases . . . . there was complete resolution of all inflammatory symptoms. In 1 instance the patient arbitrarily reduced the dose of streptomycin to 0.5 Gm. once a day, and the condition did not completely clear up with this dose. However, when the dose was increased to 1.0 Gm. a day there was complete clearing in three weeks.

"The first evidence of change for the better was observed from nine days to three weeks after the beginning of treatment, and the improvement steadily continued after cessation of treatment until the eyes showed no evidences of any activity. However, irreversible changes did not disappear; vitreous opacities remained, although vitreous haze cleared and the opacities became more circumscribed. In 3 cases lenticular opacities already well advanced when treatment was started progressed steadily until the cataracts became mature." In 2 cases with heavily scarred corneas, there were no changes in vision, although all evidences of inflammation disappeared. "These cases may all be taken as instances of irreversible changes in the eye. In all the remaining cases there was not only complete clearing of all clinical evidences of active inflammation but also a considerable restoration of vision." This varied from a minimum improvement of from 3/200 to 12/200, with irreversible opacities in the vitreous, in 1 case, to a maximum improvement of from finger counting at 2 feet (60 cm.) to 20/20—1, in another case. "In the latter case the initial visual loss was due to early, unorganized infiltrates in the cornea, a reversible change.

"The conspicuous finding in relation to the therapeutic response was the uniform, and apparently complete, control of the clinical evidences of inflammation. In the limited period of observation after cessation of treatment there have been no recurrences. The period of observation, however, has been too short to justify any conclusion on this point. However, the indications, from the evidence at hand, are that these agents have a therapeutic action in human ocular tuberculosis quite comparable to their effect in experimental animals—certainly a bacteriostatic, and probably a bactericidal, effect.

"Toxic Reactions.—Streptomycin: All patients given streptomycin were warned of the possibility of vestibular symptoms and were instructed to discontinue use of the drug on the appearance of any vertigo. Patients under immediate control were examined each week by an otolaryngologist for any evidences of vestibular irritation, and patients not under immediate control were instructed to have similar examinations made by their local specialists.

"In 4 cases evidences of vestibular irritation developed with streptomycin therapy. In 1 case symptoms developed with streptomycin, but the patient later took dihydrostreptomycin without reaction. In every case the symptoms disappeared after the drug was withdrawn. There was no instance of any residual damage to the vestibular tract and no persisting aural symptoms. With the precautions of warning the patient, weekly aural examinations and immediate withdrawal of the antibiotic on any evidence of vestibular irritation, there appears to be no significant danger in the use of streptomycin.

"Promizole: In 4 cases definite toxic reactions to Promizole occurred." In 1 case the patient took 600 Gm. of Promizole without reaction over a three and one-half month period and then exhibited weakness and malaise. "The icterus index was found to be 17.2. Promizole was discontinued, and there was prompt recovery. Two weeks later the patient recommenced use of the drug and then took 76 Gm., without symptoms. She then again complained of weakness and dizziness. The icterus index at this time was 12, and the result of the Hanger flocculation test was positive. Promizole was then permanently discontinued, with prompt recovery from all toxic symptoms. In case 4 dermatitis developed; this subsided when Promizole was withdrawn and recurred when it was again given." One patient was hospitalized during treatment. "After receiving 140 Gm. of Promizole, she had an unexplained fever and relative leukopenia. Promizole was stopped, with prompt disappearance of all symptoms. Fever and leukopenia recurred when Promizole was again given, after a week's rest. The drug was then

permanently discontinued, with prompt subsidence of the fever and a rise in the white cell count to normal. In case 12 relative anemia and leukopenia developed after administration of 500 Gm., and the drug was permanently discontinued. In another case the patient experienced slight symptoms, consisting of lassitude, headache and anorexia, after taking 156 Gm. of Promizole. Symptoms promptly disappeared after withdrawal of the drug, and Promizole was not again given. The occurrence of toxic reactions to Promizole did not appear to be related to any undue concentration of the drug in the plasma. Similarly, there was no indication of undue retention of the drug, the maximum plasma level obtained being 2.8 mg. per 100 cc. In all other cases Promizole was administered without symptoms of any kind, and in 1 case the patient continues to take small daily doses as a precautionary measure and has now received a total of over 2,000 Gm.

"Relation of Toxic Symptoms to Total Dose.—Streptomycin: In no case was evidence of vestibular irritation noticed until a minimum total dose of 26 Gm. had been reached. Other total doses for patients showing toxic symptoms were 34, 42 and 120 Gm. In all cases in which reactions occurred, the clinical improvement preceded the occurrence of the toxic symptoms." Thus, in 1 case with the minimum dose of 26 Gm. combined with 156 Gm. of Promizole, an excellent therapeutic response had been obtained before any toxic symptoms appeared.

"Promizole: The patients showing reactions to Promizole received from 98 to 600 Gm. before any toxic symptoms were noted. In each of these patients there had already been a satisfactory response to the treatment, which continued after the drug was withdrawn.

"The evidence so far amassed indicates that while toxic reactions occur in a large percentage of patients treated with streptomycin and Promizole, in no instance so far observed have the symptoms been severe or followed by any permanent residua. Moreover, in all instances the toxic symptoms were delayed and did not occur until a satisfactory therapeutic response had been obtained. It would appear therefore that with proper precautions the combined treatment with streptomycin and Promizole is reasonably safe. Since toxic reactions appear to be delayed, a therapeutic response may be expected before any toxic manifestations occur."

**Treatment of Periarteritis Nodosa** — Manguel, Mauricio and Neer, Gustavo — *La prensa médica argentina*, 36: 2402 (November 18) 1949.

The doubtful etiopathogenesis of periarteritis nodosa accounts for the lack of specific treatment. The part played by hypergia is established beyond doubt, on the basis of the more or less frequent history of allergy in the form of urticaria or asthma, the high incidence of eosinophilia, the transitory character of the clinical symptoms, the attacks of cutaneous eruptions and certain experimental findings. The development in attacks makes evaluation of any treatment difficult. As cure may be achieved in 5 to 10 per cent of the cases early diagnosis and treatment are indicated. According to several writers spontaneous cure occurs in 10 to 20 per cent of the cases. An analysis was made of 7 cases and it was concluded that contrary to the general opinion the disease is not usually fatal, and that it is often diagnosed only on autopsy. Several writers used trivalent arsenicals therapeutically, like arsphenamine. One found the serologic syphilis reactions positive in 3 cases and advised arsenical treatment. While some consider the results of arsenical treatment as encouraging on the basis of a large experience, others observed development of periarteritis nodosa during antisyphilitic treatment with neoarsphenamine. One case with sulfapyridine treatment was apparently successful; this case showed a septic course and after 39 days sulfapyridine treatment was started with an initial dose of 4.0 Gm. followed by 0.5 Gm. every 4 hours for 12 days, with a maximal blood concentration of 18 mg. per cent. After discontinuation of the drug the fever recurred and was again controlled by continued drug treatment. A total of 156 Gm. of the drug was given and the patient was in good condition 19 months later. Several writers reported cases of periarteritis nodosa apparently caused by sensitization to sulfathiazole; their attempts to produce

the disease in animals by sensitization to sulfonamides proved a failure. They consider sulfonamide treatment indicated only in the presence of intercurrent infections. Sulfapyridine and acetylcholine were used in a case with good result, but it was difficult to draw definite conclusions as the disease courses in attacks. In 7 cases failure of sulfonamide treatment was observed. It is one writer's opinion that chronic septic foci should be eliminated in periarteritis nodosa as the nonspecific sensitizing antigens would originate in such foci; he also suggests chemotherapy and desensitizing treatment. The antihistaminics have been suggested on the basis of the allergic theory of the affection but scanty or no results have been obtained, because histamine is not the mediating poison and because not all clinical manifestations have the same basic mechanism. A case was reported which responded to vasodilator and antiinfectious medication. Large doses of vitamin C were used by one writer for several weeks without success. Several others conclude that only symptomatic treatment is feasible. Another states that salicylates are ineffective against the articular and para-articular pains. Several believe it necessary at times to use opiates for pain and papaverine for peripheral arterial vasospasms.

The general condition must be considered; blood and plasma transfusions may be used for protein supply and as treatment of the anemia, and otherwise symptomatic treatment must be resorted to, in accord with the visceral disturbances.

**Aminopterin in the Treatment of Acute Leukemia** — EDITORIAL — *Annals of Internal Medicine*, 31: 1129 (December) 1949.

Folic acid antagonists have been employed on an experimental basis in the treatment of acute leukemia in many clinics. "Several different compounds have been used with more or less effect, but at present the most potent and most extensively employed is aminopterin (4-aminopteroyl glutamic acid)."

Remissions may be obtained, but the frequency of such remissions has varied greatly in different clinics.

"The reason for such divergent results is not evident. The criteria of a remission employed by various observers may differ. It is questionable whether the failure to obtain remissions is due merely to inadequate dosage, since toxic reactions were common. . . . However, the margin between an effective dose and a dangerously toxic dose is at times very narrow, and the more successful observers may have continued treatment with greater hardihood in spite of alarming toxic symptoms.

"In cases obtaining a satisfactory remission there have been marked subjective improvement, subsidence of fever and bleeding and an increase in strength so that within two or three weeks certain patients have been able to resume normal activities. There is a reduction in the total leukocyte count to normal or even to leukopenic levels. The primitive cells diminish in number or may disappear from the blood, so that it appears normal. The bone marrow tends to revert toward a normal pattern with a marked diminution in the percentage of blast cells. Some have reported that films of the marrow became normal, whereas others found some abnormality persisting. There may be an erythrocytic hyperplasia with the appearance of megaloblasts in the marrow, as might be expected with a deficiency of folic acid. With this there may be a rise in the red cell count and an increase in blood platelets. There may be a diminution in the size of the lymph nodes and spleen which is sometimes very marked.

"Such remissions may last for a few weeks or months, but as a rule aminopterin must be continued in a reduced maintenance dose or a relapse quickly follows. If a relapse occurs, resumption of a full dose may bring about further remissions. Patients have been maintained in reasonably good condition in this way for many months, and 1 case for nearly two years. Eventually, however, either they fail to respond to aminopterin or grave toxic symptoms necessitate terminating treatment, the disease progresses, and death ensues. No case has been cured. Aminopterin seems to be ineffective in chronic myeloid leukemia.

"Aminopterin is a potent and very dangerous drug, and its effects are by no means limited to the hemopoietic tissues. Toxic

manifestations are frequent and often severe. In many cases they are unavoidable if an effective dose is administered. One of the commonest is an ulcerative stomatitis which is often but not invariably associated with a leukopenia. Manifestations of a gastroenteritis are also frequent. More serious are profuse hemorrhages, especially from the nose and gastrointestinal tract, which may be uncontrollable. Leukopenia is common, and there may be an extreme granulocytopenia with increasing anemia and thrombocytopenia, associated with hypoplasia of the marrow which may be irreversible. Cutaneous eruptions have been described in severe cases. Among occasional minor manifestations may be mentioned alopecia and deafness.

"Ulcerations of the buccal mucous membranes and hemorrhages are common manifestations of the disease and do not necessarily contraindicate treatment with aminopterin. In patients who are under treatment, however, it may be difficult to determine whether such symptoms are referable to the disease or to the drug.

"Individual susceptibility to aminopterin varies, and the dose has to be adjusted for each case. Severe toxemia may appear abruptly. It often subsides, however, if aminopterin is stopped promptly and suitable treatment administered (folic acid, transfusion, antibiotics).

"There are obvious difficulties in interpreting the results of treatment in these cases. Spontaneous remissions occur occasionally in acute leukemia." The frequency with which they occur is not known precisely, but an estimate of 10 per cent is probably a maximum figure. "Furthermore spontaneous remissions as complete and long-lasting as those described in some of the reported cases are quite rare. There can be little doubt that aminopterin has favorably influenced the course of the disease and that its effect is much more definite than that of the other procedures which have been previously employed.

"It is equally evident, however, that aminopterin is a highly unsatisfactory therapeutic agent. Its action is unpredictable, and it is effective in only a minority of the cases. Its effect is temporary only, and no cure, nothing more than a transient remission can be hoped for. It causes serious toxic reactions, and some degree of such action must be anticipated if effective quantities are given. In many cases these reactions are prohibitively severe. For the present, the use of aminopterin is still experimental and should properly be restricted to clinics in which the patients can be observed with great care and corrective measures instituted promptly if serious toxemia develops. Under such conditions aminopterin may justifiably be employed since it offers a reasonable prospect of prolonging life and increasing comfort in some cases.

"The chief importance of this work is that it opens up a new field for investigation of the treatment of neoplastic diseases. Even if no more satisfactory antagonist to folic acid should be found, there are many other essential metabolic processes in the cells which might be influenced in a similar manner if the chemical reactions involved were precisely known. The hope is justified that some substance may be found which would act more specifically upon the metabolism of neoplastic cells and presumably be more effective and less damaging to other tissues."

**The Treatment of Bacillary Urinary Infections with Chloromycetin** — CHITTENDEN, GEORGE E., SHARP, ELWOOD A., VONDER HEIDE, E. C., BRATTON, A. C., GLAZKO, A. J. AND STIMPERT, F. D.—*Journal of Urology*, 62: 771 (November) 1949.

"Chloromycetin (Chloramphenicol) is a powerful new antibiotic of great value in the treatment of bacillary urinary infections."

"The bacteriologic spectrum of antibiotic activity of chloromycetin reveals that chloromycetin is highly effective in the bacillary group of organisms commonly found in both acute and chronic urinary tract infections.

"Chloromycetin has the advantage that it may be administered orally and is singularly devoid of gastrointestinal, neurotoxic, cutaneous or allergic reactions although each patient should be carefully watched for any adverse symptoms.

"In this preliminary report 50 cases have been thoroughly studied and complete case records documented. . . . Wher-

ever possible complete urologic surveys including cystoscopy, excretory and retrograde urograms, appropriate blood studies, frequent urinalysis and urine cultures as well as accessory studies were done.

"Approximately 70 per cent of the patients had been unsuccessfully treated with chemotherapy and other antibiotics prior to the administration of therapy. In addition, it was early recognized that since such a high percentage of mixed infections was encountered (65 per cent), adjunct therapy was necessary. As a result, penicillin and sulfonamides were administered whenever mixed infections were found. Likewise every effort was made to carry out surgical measures and eradicate or correct focal sources if such circumstances existed."

"Of these 50 patients, 38 had major structural urinary tract pathological changes such as calculi, prostatic hypertrophy, carcinoma or other disease states. Almost without exception these patients were clinically benefited but unless improvement was sustained they were listed as unimproved or relapsed. In fact, each of the 9 cases listed as unimproved had severe complicating pathological changes from which no permanent improvement was considered possible."

"Simple bacillary urinary infections, uncomplicated by major urologic pathological changes usually present few problems. The therapeutic response is rapid and often dramatic. The temperature, if elevated, usually becomes normal within a few hours and a grossly purulent urine becomes clear and free of leukocytes and bacilli within 24 to 36 hours. Urinary cultures likewise quickly become sterile. Dosage, however, should be adequate and patients should be followed for a sufficient period of time to determine permanent results."

"A variety of dosage patterns were studied ranging from large single doses (3.0 Gm.) to smaller doses (1.0 to 1.5 Gm.) in divided amounts from 0.25 to 0.5 Gm. at 6 to 8 hour intervals around the clock. In general it can be said that the latter (1.0 to 1.5 Gm. for 24 hours) is the optimum dosage with possibly in severe cases an initial dose of 1.0 Gm. to establish an early high serum level."

"Complicated urinary infections where coccal organisms are present require proper adjunct therapy either with penicillin or the sulfonamides. . . . Penicillin dosages also should be adequate."

"Finally, surgical dictates still prevail and the removal of calculi, obstructions, carcinoma and focal sources are necessary for the ultimate and complete control of urinary infections."

# Pediatrics

**Fatal Boric Acid Poisoning in a Newborn Infant** — ABRAMSON, HAROLD— *Pediatrics*, 4: 719 (December) 1949.

"Boric acid is not a mild and harmless drug. It is quickly absorbed into the body and, in proper amounts, may readily cause toxicity and death. In addition, boric acid exhibits a selective affinity for certain organs, such as the brain and spinal cord. When consideration is given to the extensive use of boric acid in various forms, it is surprising that more instances of poisoning have not been reported. It is possible that many cases have occurred unsuspected. Furthermore, the number of deaths from boric acid poisoning is fortunately low. These deaths may represent examples of hypersensitivity to the chemical. Nevertheless, the fatalities are needless. The doubtful benefits that are derived therapeutically from boric acid hardly justify its continued use, particularly when many more effective drugs are available."

"The following report of the death of a newborn infant from boric acid is an example."

"S. S., female, white, was born normally, full term, weight 3,825 Gm. Feedings of diluted evaporated milk were given. The early postnatal course was uneventful except for the occurrence of several loose green stools on the day of discharge to home. Twenty-four hours later, she regurgitated. The stools were loose and frequent; no blood was seen. The buttocks became reddened and excoriated. The mother applied daily to the gluteal areas unknown amounts of boric acid ointment, U. S. P. 10 per cent, and dusted liberal quantities of boric acid powder daily onto the baby's diapers.

"The symptoms became aggravated and on the eighth day of life the infant was brought back to the hospital, acutely ill and dehydrated. Signs of an early bronchopneumonia were present. Death took place 12 hours later.

"Postmortem Examination. — Gross Pathology: Skin over the baby's right shoulder showed a bullous lesion about 2.5 cm. in diameter with the edges still adherent. A similar bleb was on the left arm near the shoulder. A denuded area 9 cm. in diameter involved the skin of the vulval, anal and surrounding regions. Brain was congested. Liver was a fingerbreadth below the costal margin. It was congested and on section presented light brown mottled areas in a dark red-brown matrix. Upper part of the small intestine midway to the ileum showed no lesions. From here down to an edematous and hemorrhagic ileocecal valve, there was congestion and superficial necrosis of the mucosa. Hemorrhage and necrosis were prominent in the large gut.

"Lung surfaces and parenchyma were engorged and had small areas of mottled pink and gray. Bronchi and pulmonary vessels were congested. Kidney capsules stripped easily, leaving smooth, lobulated surfaces. On section, the upper halves of both kidneys had hemorrhages into the cortex and medulla. The remainder of the kidneys, the kidney pelves and the urinary bladder showed congestion only. The latter contained some cloudy yellow urine.

"The other organs showed nothing unusual grossly.

"Microscopic Pathology: The lungs were congested and had small foci of bronchopneumonia. Other areas exhibited thickening of the areolar septums. Liver parenchyma showed lipoid and granular degenerative changes. Kupffer cells were normal. Kidneys presented advanced nephrotic changes, with hemorrhages into the interstitial tissues of the cortex and medulla. Convoluted tubules showed granular degeneration, some cells containing detritus. Urinary bladder wall showed edema with spotty hemorrhages. Mucosa was well preserved. Mucosa and submucosa of the lower ileum were infiltrated with leukocytes and round cells. Pseudomembranous deposits were on the mucosal surfaces. Blood vessels of the small gut were engorged. Large intestine showed a similar pseudomembranous colitis and engorgement of blood vessels. In some areas, the epithelial cells of the tubular glands had disappeared, leaving superficial ulcerations of the mucosa. Brain cortex, basal gan-

glions, brain stem and cerebellum showed congestions. Spleen and the adrenal glands were similarly engorged.

"Bacteriology: Postmortem cultures from the gut and the spleen were negative for pathogenic bacteria."

The history of the use of boric acid in ointment form and as a dusting powder, the excoriated buttocks, the diarrhea and dehydration, the presence of bullous skin lesions, and the hemorrhagic phenomena seen in the kidneys and intestines suggested the possibility of boric acid poisoning. Fresh specimens of the gut and liver, and pieces of the brain, liver, and kidneys preserved in formaldehyde were sent for chemical analysis. Boric acid was found in the amount of 26 mg. in 50 Gm. of composite sample, or 0.052 per cent. This quantity represents a lethal concentration of boric acid.

**Familial Erythroblastic (Cooley's) Anemia in an American Indian Infant** — PROUTY, MARGARET — *American Journal of Diseases of Children*, 79: 99 (January) 1950.

It is the author's purpose to report a case of anemia resembling familial erythroblastic anemia (Cooley's anemia; Mediterranean disease) in an American Indian infant. "It is of especial interest because it is believed to be the first case of the condition reported in a person of this race and also because of the extremely early age at which the condition became apparent.

"First, however, there may be merit in pointing out the fact that it is increasingly evident that cases of familial erythroblastic anemia are overlooked because the attending physician fails to keep it in mind except when treating descendants of persons of the Mediterranean races."

The disease has a range from the mildest to the severest forms. "In fact, the mild forms may include no anemia at all.

"The severer forms are characterized by the production of large numbers of abnormal erythrocytes. The cells are usually described as macrocytic except when division has produced microcytes. The cells are hypochromic and appear to be irregularly stained. A striking feature is the large numbers of nucleated erythrocytes. Excessive fragmentation gives rise to numerous irregular forms."

Since the target cell was first described, the presence of such cells in persons with this disease has been well recognized. "These cells were described as having 'a central, sugar loaf elevation, so that a cross section has the appearance of a Mexican hat instead of the normal dumbbell.' On the usual stained smear these cells have a peripheral ring and center that are hemoglobin stained, but the intermediate zone is pale. The finding of these cells, however, is not limited to this syndrome."

The presence of decreased cell fragility has been confirmed.

"Besides the striking blood picture, there may be other diagnostic criteria, such as the mongoloid facies. A protruding abdomen may result from the splenic enlargement, and pallor and anorexia are not uncommon. Bone changes are serious and appear on roentgenograms as bony striae."

Report of a Case.—A male American Indian infant was first seen at the age of 2 months because of an umbilical hernia. "The rupture had been noted one month before and was rapidly becoming more prominent. The ancestry on the father's side was pure, but the mother was reported to have had a French great grandmother. There had been no abnormalities of birth, although the infant had been premature with a weight at birth of 4 pounds 7 ounces. The present weight was 8 pounds 1 1/2 ounces. Results of physical examination were essentially normal except for the hernia, which was reduced and held in place by a broad adhesive dressing. Blood counts were not made.

"The infant was returned to the hospital three weeks later with multiple complaints. For the previous week he had been crying much of the time. Abdominal distention was present; he had much flatus and loose stools for two days. There was no fever or vomiting.

"The most impressive feature was a jaundice, striking even in his copper skin. The liver and spleen were not palpable and the hernia was showing satisfactory reduction. There was no sign of an infectious process.

"The icteric index was 99.8 units. The urinary test for bile gave a faintly positive reaction, and bile was present in the stool.

"The blood presented the most interesting picture. The red blood cell count was 2,670,000, the white blood cell count, 21,900 and the hemoglobin concentration, 8.5 Gm. (51 per cent). Anisocytosis and poikilocytosis were prominent, with a tendency toward macrocytosis. There was an occasional Howell body. Reticulocytes made up 10 to 15 per cent of the total. Many cells were basochromic and the so-called target cells were common.

"In making a count of 100 white cells, 26 nucleated red cells were seen, many of which were macroblasts. The differential count was as follows: neutrophils, 17 (segmented, 11; band forms, 6); lymphocytes, 72; lymphoblasts, 2; eosinophils, 4, and unidentified forms, 5, per hundred cells.

"No sickling of the red cells was noted even under decreased oxygen tension. Tests revealed decreased cell fragility; initial hemolysis began at 0.34 per cent and was complete at 0.28 per cent (the control showed initial hemolysis at 0.44 per cent and hemolysis was complete at 0.38 per cent). A van den Bergh test was not done. Unfortunately, no roentgenograms of bone were made.

"An initial transfusion of 100 cc. of whole blood was given, followed two days later by one of 75 cc. The jaundice faded gradually during the next one and one-half weeks that he remained under observation, but the blood picture did not show much improvement. The red blood cell count did not rise above 2,900,000, and the hemoglobin concentration was essentially the same. The white blood cell count fell to 8,950, but the stained smear showed little tendency to return to normal."

The mother was confronted with a family problem which caused her to return to the reservation with the infant, and he passed from the author's observation.

From this point the author has only the statement of the local physician who did not see the patient until approximately four months later, at which time the infant was moribund. "A 'cold' had been contracted a few days previously with a complicating bronchopneumonia. No blood counts were made before his death, as the physician was not told of the previous history."

At the author's request, the physician called the mother who stated that the infant had appeared "all right" to her and was gaining weight until the infection of the upper respiratory tract occurred.

"This case presented a problem in differential diagnosis." Due to the severe jaundice and gastrointestinal complaints, the author first considered the diagnosis of an obstructive jaundice. "However, the stools were not acholic, and after the first transfusion the gastrointestinal complaints disappeared. The anemia was revealed on blood count, which directed attention to other causes.

"Erythroblastosis fetalis also had to be considered. However, the jaundice did not appear until late in the second month, and the mother, father and infant were all Rh positive.

"Hemolytic icterus was a possibility. However, the infant's blood had a diminished resistance to hemolysis by hypotonic solution and did not have the microcytosis or spherocytes usually observed.

"Sickle cell anemia was ruled out by failure to demonstrate sickling. The parents denied any Negro mixture.

"Pernicious anemia almost never occurs in infants, and this patient did not have the high color index or leukopenia usually seen in persons with pernicious anemia.

"The father, mother and infant had negative reactions to the Kahn test for syphilis.

"Chronic secondary anemia did not seem a possibility, since the condition appeared as an acute process which reached its peak after the first visit to the hospital and was not accompanied with any infectious process.

"Criteria for diagnosis of megaloblastic anemia of infancy . . . . appeared not to be satisfied in this instance.

"With familial erythroblastic anemia left as the chief possibility, the condition of the patient did not fit all the usual diagnostic criteria." The author thought, however, that absence of splenomegaly and the severe jaundice could be explained on the basis of his immaturity. "By racial characteristic this infant already had the

mongoloid-like facies that usually does not appear in the affected persons until after the first year. It is unfortunate that roentgenograms of bone were not made, but one author stated that the bone changes do not come until after the blood changes. They have been observed in infants as young as 4 1/2 months, though usually not appearing until the sixth to ninth months. With hereditary factors in mind, a count made on the mother's blood showed no abnormality. The father was not available for such a study."

**Treatment of Rheumatic Fever** — MANGUEL, MAURICIO — *La prensa médica argentina*, 36: 2449 (November 25) 1949.

The importance of the streptococcic infection in the genesis of rheumatic fever is evident and perhaps the beta-hemolytic streptococcus prepares the terrain or increases the virulence of the specific agent of rheumatic fever. The importance of the enzyme hyaluronidase in the capsule of the streptococcus and its polymerizing action on the hyaluronic acid present in the mesenchyma in the etiopathogenesis of this disease has not yet been clarified. One writer distinguishes four phases; during the first phase the patient is host to the beta-hemolytic streptococcus and is a potential rheumatic; the second phase is that of latency, lasting one to four weeks during which period hypersensitivity develops, slight fever, asthenia and leukocytosis may be present and the antistreptolysin titer increases; the third phase is that of activity of the disease, and the fourth is that of inactivity. Another writer distinguishes three phases; namely, that of acute streptococcic rhinopharyngitis and infection of the upper respiratory tract, that of the presence of hemolytic streptococci without signs or clinical symptoms during which salicylate treatment may prevent the next phase, and that of the exudative manifestations of rheumatic fever, difficult to treat, with the goal of treatment being prevention of cardiovascular involvement.

The fundamental indications of treatment during the active stage are rest and salicylates. Absolute early permanent and sufficiently prolonged bedrest is indicated even in the mildest cases. Apyrexia does not exclude activity of the process. The initial polynuclear leukocytosis is transformed later into relative lymphocytosis; leukocytosis may be lacking in cardiac forms without arthritis. Tachycardia should always be watched and is improved by rest, but a normal heart rate does not definitely imply disappearance of activity of the process. The sedimentation rate is a more sensitive index of activity of the process but does not have an absolute value either. According to one writer in some cases the sedimentation rate remains high and tachycardia persists in spite of bedrest and salicylate treatment, but these signs disappear soon after treatment is discontinued. Signs of carditis include tachycardia, precordial pain, gallop rhythm, dulling of the first sound, cardiac enlargement and electrocardiographic alterations; endocarditis should be diagnosed with caution during the acute stage unless a murmur is diastolic or persists for more than six months if systolic and does not change with position or respiration or becomes accentuated and is transmitted. The sedimentation rate may be exceptionally normal in carditis. Transition from bedrest to normal activity must be gradual, and may be based on exercise tests. Profuse perspiration requires alcohol and vinegar rubs, with protection against catching colds. The diuresis must be maintained by a sufficient fluid intake, and the diet should be adequate.

Salicylates have a definite antifebrile, analgesic and antiphlogistic effect and control fever and arthritis within two to three days and improve the general condition, but it is generally believed that they do not modify the process or prevent or influence the cardiac complications, although one writer takes issue with the latter contention, and claims that salicylates have a specific effect impeding the antigen-antibody reaction of rheumatic fever. The reaction between salicylic acid and the aseptic inflammatory process would be indicated by the fact that elimination of conjugated salicylates is increased in active and that of free radicals in convalescent rheumatics. One writer bases the treatment on the blood salicylate level. It has been demonstrated that hyaluronidase is inhibited by salicylate, diminishing the

permeability of the connective tissue. The proliferative reaction producing valvular damage is not impeded by the drug. One writer found cardiac involvement in 30 per cent of 63 cases treated with low doses, and in none of 38 cases treated with high doses. Some authors claim an antiallergic effect of salicylates, but only during the period of sensitization. The dosage in children ranges between 0.5 and 1.2 Gm. per day per year of life. One writer advises intravenous injection in saline solution. Addition of bicarbonate favors tolerance in peroral treatment. It has been shown that the salicylemia is higher when paraamino benzoic acid or ammonium chloride is given simultaneously. A plasma level of 35 mg. per cent is considered useful. South American authors advise lower concentrations. The intravenous route does not seem to be superior to the peroral one, and is more risky and difficult. Rectal administration may be used supplementary. Intramuscular, subcutaneous and intraduodenal administrations have also been suggested. Salicylate resistance of rheumatic fever is not admitted by all authors. Salicylate treatment should be continued for two weeks after disappearance of symptoms, and longer in the presence of carditis; in general moderately severe cases require salicylates for 45 days and severe ones for a longer period of time.

The manifestations of salicylate intoxication are in mild cases nausea, vomiting, epigastric burning, tinnitus, vertigo and hypacusia; in moderately severe cases they are allergic manifestations, hemorrhages, hematuria and purpura, and in severe cases they are delirium, coma, dyspnea, acetonuria, and cardiovascular symptoms. Alkalosis rather than acidosis is responsible for salicylate poisoning according to newer conceptions, and reduction of the alkaline reserve occurs in either alkalosis or acidosis, and is caused by hyperventilation from stimulation of the respiratory center. Thus simultaneous bicarbonate administration seems unjustified and diminishes the salicylemia, either by making intestinal salicylate absorption more difficult or by increasing the extracellular fluids which on reabsorption diminish the blood level, or by increasing the renal salicylate elimination. Glucose with or without insulin is indicated in salicylate poisoning. Hemorrhagic phenomena correspond to a certain degree of hypoprothrombinemia and are controlled by vitamin K, 1 mg. of which impedes the hypoprothrombinemic effect of 1 Gm. of salicylic acid, but there is no unanimity of opinion in this respect.

When salicylates cannot be used pyramidon may be resorted to as its toxic doses are farther from the useful ones, but it carries the danger of agranulocytosis; the latter seems more frequent in North America than in South America. The dose is up to 3 Gm. daily, in individual doses of 0.3 Gm. It diminishes vascular permeability, does not produce allergic phenomena, and has no effect on the myocardium. It is considered highly useful in chorea of children. It has been given intravenously but may cause immediate nervous reactions in this way. Sodium gentisate has the same effects as the salicylate and is its oxidation product. A double calcium salt of benzoic acid and benzol ester succinic acid has been used and the succinic acid which is a catalyzer is believed to prevent inhibition of certain oxidative reactions and to act as a reducing agent of the block of certain respiratory enzymes. Vaccinotherapy is ineffective and acts only as pyretotherapy or proteinotherapy. Recently Henoch's compound E has been used successfully. Sulfonamides are useless and may even be harmful. Convalescent serum has been used but may produce reactions. Vitamins C and P have also been used. Precordial roentgenotherapy is useless. Heart failure should be treated in the usual way, but digitalis should be used cautiously and in smaller doses. Chorea requires salicylates, sedation of the nervous system with barbiturates or magnesium sulfate, and rest; pyretotherapy has also been recommended. Codeine rather than morphine should be used for precordial pain.

During the latent stage intermittent salicylate treatment has been advised. Many authors recommend protracted sulfonamide treatment for prevention of recurrences and reduction of streptococcic infections of the upper respiratory tract in a daily dose of 1 Gm. throughout the winter season; a blood level of 2 mg. per cent seems appropriate. Toxic manifestations may occur and discontinuous treatment has been advised. Once a streptococ-

cic infection is present rheumatic manifestations are not prevented by the sulfonamides.

Penicillin is useless in rheumatic fever and may be harmful as products of lysis of streptococci may aggravate the condition.

Eradication of septic foci is not justified during rheumatic activity as it may be harmful and does not cure the rheumatic fever. Postoperative bacterial endocarditis may result. Elimination of septic foci should be postponed for at least six months after rheumatic activity has subsided and antibiotics should be given before and after operation, but sulfonamides may be used instead. The author is not inclined to recommend tonsillectomy prophylactically. A cold and humid climate should be avoided and subtropical areas are preferable. Medicosocial treatment is of great importance, with creation of proper clinics. The patient or his family should be instructed concerning proper hygiene and diet, avoidance of colds and places where large numbers of people congregate, and consultation of a physician whenever asthenia, anorexia, weight loss or fever appears; periodic examinations are indicated. Rheumatic fever is a chronic recurrent disease, capable of incapacitating the patient by cardiac involvement.

**Chloramphenicol in Treatment of Infantile Gastroenteritis. A Preliminary Report** — Rogers, K. B., Koegler, S. J. and Gerrard, John — *British Medical Journal*, 2: 1501 (December 31) 1949.

*Bact. coli* B.G.T. (Bray-Giles-Taylor) has been found to be intimately associated with epidemic infantile gastroenteritis. During the last 10 months one of the writers has studied the appearance of this organism in 86 infants under the age of 1 year admitted to the Birmingham Children's Hospital. "Routine rectal swabs were taken on admission and in many cases five days later, and again if a case of gastroenteritis appeared in the ward. The first isolation of the *Bact. coli* B.G.T. from the stool was noted and the subsequent progress of the infant observed."

"The enteritis did not respond to the administration of sulphonamides, penicillin, or streptomycin, but the response, both clinically and bacteriologically, to chloramphenicol has been most encouraging."

Fifteen cases were treated with chloramphenicol. Of the 15 one died (case 1) and the other 14 are living.

"It is felt that the results with this antibiotic are hopeful enough to warrant a preliminary communication, although it is realized that the number treated is small." Results can best be illustrated by the following case histories.

Case 1.—"A girl aged 6 months was admitted with scalded buttocks, and developed gastroenteritis associated with the isolation of *Bact. coli* B.G.T. while on penicillin, sulphonamides, and streptomycin. . . . In spite of treatment with sulphonamides, penicillin, and streptomycin her gastroenteritis continued, but within five days of starting chloramphenicol *Bact. coli* B.G.T. disappeared from the stools and the diarrhoea ceased. Unfortunately she died from complications due to burns nine days after the disappearance of *Bact. coli* B.G.T. from the faeces. A postmortem examination was not made."

Case 2.—"A boy aged 5 weeks was admitted with meningococcal meningitis. Nineteen days after the first appearance of *Bact. coli* B.G.T. in the stools, and while receiving both sulphonamides and penicillin, he developed a severe gastroenteritis. No improvement followed the administration of streptomycin, but within three days of starting chloramphenicol therapy the diarrhoea ceased; a day later *Bact. coli* B.G.T. disappeared from the stools. Further recovery was uneventful."

Case 3.—"A boy aged 8 months was admitted with pink disease. Fifteen days after admission he developed gastroenteritis associated with the isolation of *Bact. coli* B.G.T. from the faeces. With penicillin and sulphonamide therapy there was little improvement, but on chloramphenicol the organism disappeared within eight days, the diarrhoea ceased, and he started to gain weight satisfactorily."

Case 4.—"A girl aged 4 1/2 months was admitted with thrush and a left parotitis. The infection subsided with the application of gentian violet locally and penicillin systemically, but 10 days after the isolation of *Bact. coli* B.G.T. from the stools she developed diarrhoea and lost

12 ounces in weight in three days. The enteritis did not respond to symptomatic treatment, but when chloramphenicol was given the diarrhoea ceased; *Bact. coli* B.G.T. disappeared from the stools in five days.

"In 8 additional cases the administration of chloramphenicol, in conjunction with intravenous alimentation where necessary, and graded feedings, was followed by rapid amelioration of the diarrhoea, and *Bact. coli* B.G.T. could no longer be recovered from the faeces. In 3 cases there was a bacteriological relapse, although no case had a recurrence of the diarrhoea.

"Carriers.—Three children who had had diarrhoea associated with the presence of *Bact. coli* B.G.T. but had recovered from their diarrhoea still excreted this organism in the faeces. They were given chloramphenicol. In 1 case *Bact. coli* B.G.T. was not recovered from the faeces after the third day of treatment. In a second the organism was not recovered from the fifth day of treatment until four days after the cessation of treatment, when a bacteriological relapse occurred. In the third case this organism was still present in the faeces after nine days' treatment.

"Clearance of the Organism.—The average time for chloramphenicol to effect a clearance of *Bact. coli* B.G.T., except in the carriers . . . . was four days, within the limits of two and eight days. In 2 cases the organism reappeared in the faeces 1 and 7 days after cessation of treatment which had lasted 7 to 11 days respectively, but the organisms were still sensitive to chloramphenicol. These cases may have been either true relapses or reinfections, as neither had been discharged from the infected ward.

"Parenteral Infection.—Six cases were admitted with an otitis media. No *Bact. coli* B.G.T. were isolated from their faeces, but before these infants were fit for discharge they had not only acquired the organism but had also developed gastroenteritis. It is understandable that, in the absence of recognition of any organism as a potential pathogen in the stools, the diarrhoea might be ascribed to the inflammation in the ears. In point of fact, the sequence of events would seem to have been an initial infection necessitating admission to hospital, followed by a subsequently acquired intestinal infection. An otitis media was present at the onset of the gastroenteritis in 2 cases; in 3 additional cases an otitis media developed from 5 to 10 days after the onset of the gastrointestinal infection. In no case was *Bact. coli* B.G.T. isolated from the middle ear."

The following case is worthy of special mention as it was the only one in which a primary urinary infection with *Bact. coli* B.G.T. was encountered.

"A boy aged 7 weeks was admitted with anaemia, mild jaundice which developed during the week before admission, severe urinary tract infection, and bilateral otitis media. The urine contained many pus cells, casts, and a few red cells, and gave a heavy pure growth of *Bact. coli* B.G.T. There was no evidence of any abnormality in the blood apart from anaemia. Gastroenteritis developed three days after admission, but *Bact. coli* B.G.T. were not isolated from the faeces. The urinary infection was not influenced by penicillin, given on account of the otitis media, or by sulphonamides, but responded dramatically, as did the enteritis, to chloramphenicol."

*Bact. coli* B.G.T. may be associated with diarrhoea in older children; the oldest child known to be affected in the writers' hospital was a girl 4 years old.

"Chloramphenicol is marketed in 250 mg. enteric-coated capsules, but as infants cannot swallow these the drug has been given as a suspension with tragacanth flavoured with syrup of raspberry and chloroform water. The babies have needed little encouragement to take it in spite of its bitter taste. The dosage given has been 75 mg. per pound (165 mg. per Kg.) body weight per day in 6 or 8 divided doses; the initial dose was twice the maintenance dose."

"The administration of chloramphenicol has occasionally coloured the stools bright green. Four of the cases developed sore buttocks followed by a spreading generalized dermatitis which cleared only after two weeks, but it is not established that chloramphenicol was responsible. Apart from this possible toxic reaction, no untoward effects have been noted; routine blood counts and urine examinations on all cases have shown no abnormalities."

"A trial with chloramphenicol is now being undertaken on all severe cases of infantile gastroenteritis, irrespective of the presence of the known specific strains of *Bact. coli*. Although *Bact. coli* B.G.T. is often associated with gastroenteritis there is no proof of its actual pathogenicity, and, moreover, a number of babies who excrete this specific strain of *Bact. coli* never develop symptoms: there may have been a previous undetected infection with *Bact. coli* B.G.T. in these cases. On the other hand, an appreciable number of children are admitted with primary gastroenteritis without any identifiable specific strain of *Bact. coli* in their faeces.

"Bacteriology.—Routine Examination: Faeces from cases of gastroenteritis were examined to exclude the presence of protozoa and cultured on Leifson's desoxycholate citrate medium as well as in selenite enrichment medium to exclude the presence of salmonellae and shigellae. A MacConkey plate was also inoculated and at least four representative colonies were tested by slide agglutination, using Bray and Beavan's technique, which gave very clearcut and reliable results." All positive colonies were inoculated into sugars.

"Sensitivity of the Organism to Chloramphenicol: *Bact. coli* B.G.T. was inhibited in concentrations of chloramphenicol varying between 2 to 4 μg./ml. Tests were made using representative colonies from each specimen from which *Bact. coli* B.G.T. was isolated while the child was on chloramphenicol treatment or if the organism reappeared after treatment had been stopped. No change in sensitivity of the organism was shown in these experiments. . . . This result is very different from those obtained with streptomycin, when insensitive variants began to appear in nearly all cases within 24 hours of the initiation of treatment. In most of the antibiotic-treated cases specimens of faeces were obtained once or twice daily during treatment and daily for two weeks after its cessation or until the patient was discharged.

"Blood Levels: Estimations of chloramphenicol blood levels were made; the technical difficulties were not fully overcome, but by the use of a modification of the technique described by Fleming and Smith levels up to 120 μg./ml. were obtained." The test organism used was a strain of *Bact. coli* B.G.T. from case 1. "There seemed to be definite individual variations in the absorption of the drug by the patient, so a relatively high dose of chloramphenicol was employed."

**Peptic Ulcer in Infancy and Childhood. Report of 3 Cases** — TUDOR, ROBERT B. — *Minnesota Medicine*, 33: 57 (January) 1950.

"The etiology of peptic ulcers in infants and children in the majority is obscure. Prematurity has been mentioned as a cause. Cases have occurred in association with erythroblastosis fetalis. . . . There may be an association between the development of ulcers and the onset of hydrochloric acid secretion in the stomach. The acidity of the gastric juice reaches a maximum within 48 hours of birth, when it is equivalent to that of an adult. Thereafter, it falls rapidly and remains low during infancy. Ulcerations have been reported in association with stenosis of the intestinal tract. They have also occurred during the course of hepatic disease, pancreatic disease, and erythroblastosis. Two cases have followed trauma, 1 following external trauma, and 1 following aspiration of the newborn respiratory tract. For years the association between severe systemic infection and peptic ulceration has been appreciated. Many organisms, including streptococci and tubercle bacilli, have been cultured from these ulcers. Extensive body burns are many times followed by peptic ulcers, probably because of the infection which is usually also present. Stimulation of the diencephalon will produce hyperemia of the gastric mucosa and will increase gastric motility, hypertonus and hypersecretion. In the adolescent group peptic ulcer may be a psychosomatic disease. It has been suggested that there is a possible association between the anterior pituitary gland and peptic ulcer in adolescent boys.

"Ulcers in the newborn, in whom the symptoms become outstanding within the first two weeks of life, have special characteristics. The great majority bleed seriously or perforate. In many the onset is precipitous without recognizable symptoms or signs. Except in a few cases neither clinically nor at autopsy is there evidence

of intracranial injury or localized or generalized sepsis. The lesions are acute.

"During the first 24 months of life beyond the newborn period, the nature of the disease changes. Although again the great majority of ulcers bleed grossly or perforate, there are often premonitory symptoms, such as refusal of feedings, evidence of abdominal pain, vomiting, occasional streaking of blood in the vomitus, sometimes occurring over a period of weeks or months before the onset of graver symptoms. Persistent pylorospasm or inflammatory or cicatricial pyloric stenosis is seen occasionally. Many of the patients are septic and marasmic.

"Between the ages of 2 and 6 years recognized examples of peptic ulcer are very few.

"As age advances beyond the seventh year, there is a rise in the number of cases recognized, with special accentuation on pyloric stenosis and perforation. Hemorrhage recedes into the background. Among the cases reported in this age group, the symptoms have often been present intermittently or continuously over a period of months or years.

"Hemorrhage from stomach or bowel is the most characteristic sign of peptic ulceration in children. In the series of cases here reported, bleeding occurred in 48 per cent of the children under 1 year and in 29 per cent of the total series. Duodenal ulcer may cause spasm of the pylorus, so that the condition may suggest pyloric stenosis. Regardless of the age of the child, a complaint of epigastric pain occurring sometimes after meals, particularly at night, relieved by the ingestion of milk or other food or by emesis, and accompanied by tenderness in the abdomen, should lead to a very strong suspicion of peptic ulcer. Indefinite abdominal discomfort, particularly if epigastric in situation, even if unaccompanied by other characteristic symptoms, may be caused by ulcer. Hyperchlorhydria is absent usually.

"Pathologically, the ulcers seen in childhood are similar to those seen in adults. If they are chronic in type, the appearance in no way differs from that of chronic ulcers in adults. A striking feature in all acute ulcers is the absence of inflammatory reaction, the lesion being purely destructive. Duodenal ulcers invariably occur above the ampulla of Vater and are generally situated on the posterior wall."

Of 286 cases of peptic ulcer, 283 collected from the literature and 3 of the writer's cases, 218 were duodenal and pyloric and 68 were gastric, a ratio of 3 to 1. "Operations were performed in 123 patients. Indications for operation were pyloric stenosis, perforation, hemorrhage and uncontrollable symptoms."

Case 1.—P. L. Z. was a white, male infant. "The birth was apparently normal. The baby nursed normally and seemed to be doing well until the fifth day of life, when the abdomen became suddenly distended. At that time the child became cyanotic and very dyspneic. The temperature was 100.4° when the child arrived at the hospital. The child was in extremis when first seen. X-ray showed a large amount of air in the peritoneal cavity with the diaphragm displaced upward. The child expired one hour after admission to the hospital.

"Postmortem examination showed a perforation of the upper end of the stomach through the greater curvature, through which gastric contents were escaping. The perforation measured 15 by 18 mm. in diameter. The other abdominal organs were normal. There was partial atelectasis of both lungs."

Case 2.—T. E. was a white male who was born one month prematurely. "Birth weight was 5 pounds 2 ounces. On the second day of life he began vomiting bile. He passed meconium per rectum which contained squamous epithelial cells. The gastrointestinal x-rays showed a dilated bowel. On admission to the hospital he was an emaciated, jaundiced white male who had a feeble cry. There was moderate dehydration. Examination was essentially negative except for a distended abdomen. Chest x-ray was negative. The K.U.B. film showed a dilated large and small bowel with fluid levels. The baby was Rh negative. Hemoglobin was 116 per cent, and the white blood cell count, 8,200. The urine showed 3-plus albumin with 6 to 10 red cells and no sugar. Barium enema showed a stenosis of the sigmoid.

"A transverse colostomy was done on the fourth day of life. The patient did well until the twentieth day of life. He was maintained with blood transfusions and

given formula orally. The distal colon was irrigated with saline and mineral oil. The colostomy worked well at all times. He began passing blood from the proximal colostomy on the twenty-third day of life. Shortly after this he became distended and expired suddenly. Postmortem examination showed a perforated duodenal ulcer and a stenosis of the sigmoid."

Case 3.—A. B. was a 14 year old white male who had been complaining of abdominal pain since he was 7 years old, and did not care to eat, especially at breakfast. "Shortly after the pain began he had a tonsillectomy and adenoidectomy. In about six months he began losing weight and the pains seemed more severe. He would sometimes vomit intermittently for a month. He seemed to crave milk and chocolate. When the pain became severe, he would lie down, as he could not stand. His appendix was removed when he was 11 years old, without influencing the course of his illness. By the time he was 12, he had become very nervous and would eat very little because he said 'his stomach did not feel like it needed food.' The pain continued until when first examined he had been vomiting for two months. He never had melena or hematemesis.

"The family history was interesting in that both mother and father felt they had stomach trouble.

"The patient was a well developed, fairly well nourished, white male. The temperature was 99°. Weight was 73 pounds. Blood pressure was 100/70. The skin was moderately dehydrated, but there was no general glandular enlargement. Head and neck were normal. The fundi were normal. Ears, nose and throat were normal. The heart and lungs were normal. The abdomen was diffusely tender. Genitalia were normal. Rectal examination was negative. Extremities were normal. Neurological examination was normal. Accessory clinical findings: hemoglobin, 88 per cent; urine normal; white blood cell count, 9,050. Stool specimens were negative for occult blood on four occasions. Intravenous pyelograms were normal. Gastrointestinal x-rays showed the duodenal bulb to be markedly deformed, with an ulcer crater in the center of the bulb and a second crater in the distal portion of the bulb. The patient fainted twice during the examination. Analysis of the gastric content showed free hydrochloric acid of 23 degrees and combined hydrochloric acid of 15 degrees.

"He was treated with bed rest, small blood transfusions, 1:5,000 atropine sulfate, amphojel, multiple milk feedings and a bland diet. On discharge from the hospital his weight was 80 pounds. The gastric analysis at that time showed free hydrochloric acid of 28 and combined hydrochloric of 14 degrees.

"On his last examination three months after his admission to the hospital, his weight was 85 pounds, and the hemoglobin was 81 per cent. He was feeling very well and had no complaints. X-rays at this time showed some irritability and deformity of the duodenal bulb, but no definite ulcer crater was noted."

**Mercury Poisoning from Calomel Producing Subacute Acrodynia and Its Treatment with Dimercaprol. Report of a Case** — CARITHERS, HUGH A.—*Pediatrics*, 4: 820 (December) 1949.

"Mercury poisoning is not uncommon. Calomel as a cause is, however, rare, not only because the drug is infrequently used in modern therapy but also because its toxicity is largely independent of the size of the dose."

"The case of mercury poisoning presented here may represent a preacrodynic state, showing many, but lacking some, of the characteristics of the disease.

"Case Report.—G. A., a girl, was first seen at the age of 6 months with the chief complaint of 'weak eyes.' She was the only child of a 21 year old mother; family history was noncontributory. Birth weight was 4.3 Kg. and delivery normal. She had been given evaporated milk formulas since birth. Vitamin complements had been started at 1 month and cereals, fruits and vegetables at 3 months.

"Child had been well until restlessness, attributed to teething, developed at 4 months of age." "Teething Powders" were given from that time until she first was brought to the writer's office, starting with ½ powder in the morning and ½ in the afternoon. "Later a whole powder was used as a dose. They were given intermittently, four or five days regularly with two or three days' rest in between. Ten

days before the patient was examined, lethargy alternating with restlessness of considerable degree was noted. Eyes appeared weak and in a few days she would not open her eyes outdoors and turned her head away from a window when indoors. She was taken to an ophthalmologist, who could find no cause for the photophobia. Temperature, checked once, was 37.7° C."

Five days before patient was brought for observation, a rash developed on the head. "There were discrete papules at first, but some soon became pustular. Another physician had prescribed a sulfonamide, which did not seem to cause local or general improvement after 48 hours. It was noted at this time that she had lost 240 Gm. in weight. She was admitted to . . . . hospital."

"Patient was a restless white infant girl, well developed and plump, but with strikingly flabby musculature. Pulse rate was 140/min., respirations were 47/min. and blood pressure was 118 systolic and 88 diastolic. She had pronounced photophobia, holding her face against her mother's neck or holding the backs of her hands pressed against her eyes if carried to a window. There was present a maculopapular rash on the head only, with a smooth, flat erythematous lesion about 3 cm. in diameter on the left brow and another of the same size just proximal to the left ankle. There was no erythema of the hands and feet and no desquamation. Fontanel was under normal tension and of normal size for her age. Eyes, except for photophobia, showed no abnormalities, there being no conjunctivitis or abnormal pupillary reaction. Examination after use of a mydriatic showed normal eyegrounds.

"In the mouth there were no abnormalities; 2 lower central incisors were present and no evidence of infection, lead or mercury line, or salivation was noted. Ear canals and drums appeared normal. Chest was symmetric. Lungs were clear and resonant. Heart rate was variable, from 90 to 140/min. Heart sounds were of good force and there were no murmurs. Abdominal musculature was markedly flabby and there were no masses or tenderness. Liver was not palpable and the tip of the spleen barely so. Genitalia were normal. Extremities were normal except for lack of muscle tone. Reflexes showed no abnormalities."

"Blood Kahn test gave negative results. Blood cell count was Hgb. 12.1 Gm./100 cc., RBC 4.1 million/cmm. and WBC 8.1 thousand/cmm. with segmented neutrophils 39 per cent, juveniles 9 per cent, lymphocytes 46 per cent, monocytes 4 per cent, eosinophils 1 per cent and basophils 1 per cent. Several routine urinalyses showed no abnormalities. Examination of the stool for ova and parasites gave negative results. Reaction to a tuberculin patch test was negative. The day after admission, a specimen of urine collected in a mercury free container showed a mercury content of 0.33 mg./1. This high figure was reduced to 0.21 mg./1. in a specimen collected eight days after admission. Eleven days after admission a specimen showed 0.05 mg./1. Roentgenogram of the long bones showed normal growth and development for the age of 6 months. Slight decalcification was evident."

"The day following admission, a 10 per cent solution of BAL in peanut oil was started. For five days patient received 0.2 cc. every four hours intramuscularly. On the sixth day, the same dosage was given every 8 hours and on the seventh day every 12 hours. Total dosage of the drug was 0.86 Gm. Because of the pustular rash, penicillin 300,000 units in oily solution was given daily, beginning on the sixth day and continuing until discharge. Full feedings with vitamin complements were given throughout the period of hospitalization."

"The great irritability and anorexia noted during the first few days of the patient's 13 day hospital stay quickly improved. Weight on admission was 7.5 Kg. By the sixth day it was 7.8 Kg. Photophobia improved slowly but was still present, to a slight degree, on discharge. Skin condition became worse after admission, more of the papules on the head becoming pustular. This cleared after penicillin was started on the fifth hospital day. The large, flat erythematous lesions, which may have been exaggerated reaction to insect bites, disappeared after a few days. At no time was there fever and the blood pressure at the time of admission was the highest recorded. Child sat alone, for the first time, toward the end of her hospital stay."

"When seen two weeks after discharge, patient still had photophobia to a moderate degree, although it had been noted that at times it seemed to be absent. There was slight desquamation of the tips of the fingers. Child had recovered from a severe infection of the upper part of the respiratory tract, which was noted the day after discharge from the hospital. She had gained only 0.17 Kg. during the two weeks at home. Thereafter, she rapidly lost all evidence of illness and one month after discharge all evidence of photophobia had disappeared. She became cheerful, ate well and at the age of 8 months weighed 8.4 Kg."

**Measles Encephalitis. Study of 50 Cases** — Sawchuk, Steven, LaBoccetta, Alfred C., Tornay, Anthony, Silverstein, Alexander and Peale, Augustin R. — *American Journal of Diseases of Children*, 78: 844 (December) 1949.

"During the winter and spring of 1946 a severe epidemic of measles took place in Philadelphia. As is usual in epidemics of this disease, there was an increase in the number of complications, one of which was encephalitis. Thirteen thousand and thirty-seven cases of measles were reported to the Health Department." The cases of the last 50 patients with measles encephalitis are reviewed and analyzed.

It was the writers' impression from the clinical and necropsy observations that edema of the brain was responsible in a great measure for the symptoms and fatal outcome in several of the patients. Dehydration therapy was instituted in some of their patients in an effort to correct cerebral edema and to study its effects on the symptoms and prognosis of the disease.

"The diagnosis of measles encephalitis was based on several symptoms. These signs were coma, convulsions, stupor or drowsiness, with or without spinal fluid changes. In this series there were patients who had transitory and bizarre neurologic responses with spinal fluid changes and they were classified as having measles encephalitis."

"In the series of 50 patients 16 died, a mortality rate of 32 per cent. There was a total of 14 cases in 1946 with 6 deaths, a mortality of 42.8 per cent in this group. Prior to 1946, 10 deaths occurred among 36 patients, a mortality rate of 28 per cent.

"In the series of 50 patients 42 per cent were boys and 58 per cent girls. Of the 16 who died, 4 were boys . . . . and 12 . . . . were girls. The ratio of the mortality from measles encephalitis in the girls to that in the boys was 3 to 1.

"Many of the patients had complications in addition to the measles encephalitis. Eighteen patients had pneumonia with an associated encephalitis. In this group there were 8 deaths. . . . The relationship of the white blood cell count to pneumonia and to encephalitis was also investigated. The median leukocyte count in those with encephalitis was 14,286 cells, with a predominance of neutrophils. Of the patients, 73 per cent had 10,000 or more white blood cells. The median leukocyte count in those with pneumonia and encephalitis was 14,167 cells; 67 per cent of these patients had 10,000 or more white blood cells. There was little difference in the leukocyte count in the patients with measles encephalitis with or without pneumonia."

Nine patients were in coma. Three of these patients in coma died. Seven patients had convulsions and 3 of these died, a mortality rate of 42.8 per cent. Twenty-two patients of those with measles encephalitis had coma and convulsions; 10 of these died, a mortality rate of 45.4 per cent. The chances for survival are less when measles encephalitis is accompanied with convulsions.

"Further analysis of the statistics showed that encephalitis was most likely to occur from the fourth to the sixth day after the onset of measles. In more than 84 per cent of the patients encephalitis developed from the third to eighth day of measles. The earliest onset was on the first day of measles, and the latest occurred on the fourteenth day."

There was an irregular age distribution of those up to 5 years of age. "Of the patients, 48 per cent were from 5 to 8 years of age inclusive." An unusually high ratio of girls was seen in this group, they comprise more than 71 per cent of the patients.

"Twenty-nine patients had 50 cells or less in the spinal fluid. There were 11 deaths in this group, or a rate of 38 per cent, the highest death rate among the groups, according to distribution of patients by spinal fluid cell count. From this observation it may be assumed that a low spinal fluid cell count in measles encephalitis indicates a grave prognosis." Further evidence for this was indicated by the fact that 75.8 per cent of the deaths in these patients with a low cell count were in the group with less than 25 cells in the spinal fluid.

"The following values are normal for the spinal fluid in the laboratory of the Philadelphia Hospital for Contagious Diseases: protein, 15 to 45 mg., sugar, 50 to 80 mg., and chlorides, 700 to 750 mg., per hundred cubic centimeters. On the first examination, the spinal fluid showed a predominance of polymorphonuclear forms in 5 patients. Two of these reverted to a lymphocytic predominance on the subsequent examination, while the remaining 3 patients still showed a predominance of polymorphonuclear forms."

An unusually large number of patients were seen with a low chloride level. No information is available regarding the chloride level in this disease.

"Dehydration therapy comprised the limitation of fluids given by mouth and the administration of hypertonic glucose solution intravenously, hypertonic magnesium sulfate enemas and concentrated human plasma intravenously. Because of the danger of complicating bacterial infection, prophylactic chemotherapy was instituted early in the disease. Except for sulfonamide drugs, used in a few of the early cases, penicillin was the drug of choice."

When the results of dehydration therapy were compared with those of nondehydrating therapy it was evident that the small difference in the percentage of mortality was not statistically significant. It was the writers' clinical impression that in certain instances, dehydration therapy prevented further involvement of the brain but this was not so in every case.

"Of the series of 50 patients, 34 were alive at the time of this study. Nineteen of the living patients returned for an interview and examination. All these patients had a complete neurologic and psychologic examination, and the majority of them had an electroencephalogram made as well. None of the patients had abnormal movements of either their upper or their lower extremities.

"Five patients of the 19 had a history of convulsions since they were discharged from the hospital. One of the 5 had petit mal attacks five years after the attack of measles encephalitis; 1 had jacksonian type convulsions, and the remaining 3 had generalized convulsions.

"Seven of the 19 patients had normal neurologic findings in the extremities, whereas 12 had normal cranial nerves as determined by the examinations.

"Two patients had evidence of cerebellar dysfunction. The presence of this condition in a third patient was not certain. Two other patients had lower motor neuron involvement; 6 patients had signs of upper motor neuron damage, and 1 exhibited signs of disease of the extrapyramidal tract. Four of the 19 patients had facial palsy of central origin. One patient had involvement of the ocular muscles which was not present before the encephalitis. One had pathologic changes in the retina, and another had diffuse lesions of the cranial nerves.

"Six patients showed abnormality of gait. Difficulty with gait was caused by cerebellar ataxia in 1, involvement of the pyramidal tract in another and lower motor neuron lesions in 4.

"Of the 19 patients, 13 had had an electroencephalographic examination. The records of only 4 of these were normal. Fourteen patients had a psychologic examination; 5 of the 14 were designated as feebleminded. One child was definitely demented, with an intelligence quotient which classified him as an idiot. The remaining children were mentally defective or showed personality changes. One child with an intelligence quotient of 131 had some personality disorder, but whether this was the result of the encephalitis or was caused by the tension that existed between her and the mother could not be ascertained.

"Information about 3 patients who were under private care was supplied by the private physicians. One of these children was apparently normal; another child was

epileptic with deterioration of the brain, and the third child had lost one year in school."

"The following conclusions were made from the results of the neurologic and psychologic examinations:

"1. Of the 19 patients examined, only 2 were normal, psychologically and neurologically.

"2. The greatest number of neuromuscular disorders involved the extremities; most of the others involved the cranial nerves. The disturbance involved either the extremities alone or the cranial nerves alone, or both.

"3. Each child with mental deficiency had also one or more neurologic abnormalities.

"4. Four of the mentally defective patients had electroencephalograms made, 3 of which were abnormal."

**Acute Appendicitis in a Premature Infant Aged 3 Weeks** — ENGSTRÖM, C.-G. — *Acta paediatrica*, 37: 355, 1949.

Appendicitis is rare in early childhood, and particularly in newborns and young infants. A small number of cases of prenatal appendicitis and appendicitis in prematures and newborns is on record, however.

The author's case concerned a premature boy with a birth weight of 1,290 Gm.; pregnancy and delivery had allegedly been normal. The infant was debile but not cyanotic and was treated with oxygen, stimulants when necessary and maternal milk by sound. During the first week of life the infant vomited mildly and was at times cyanotic on feeding, but showed a relatively good general condition and a normal weight curve. During the second week the general condition became worse, and rhinitis and pulmonary rales indicated an infection; several attacks of asphyxia supervened, during which the infant seemed moribund. Penicillin, stimulants and intramuscular blood injections were used. After a few days the condition improved, vomiting subsided and the stools became firm. On the eighteenth day the condition suddenly changed markedly; the infant was apathetic and showed decreased tonus and a pale cyanotic color. While before that day only slight meteorism had been present, on this day the abdomen was distended and a right inguinal hernia which had been readily reducible before then felt tense and firm and could not be reduced; vomiting supervened and because of the danger of strangulation a surgeon was consulted who succeeded in reducing the rupture. During the subsequent three days the condition improved with administration of fluids and plasma, and there seemed to be no indication for surgical intervention. There was some diarrhea but no vomiting, and the abdomen was meteoristic but soft. The serum proteins decreased. On the twenty-fourth day of life the general condition became rapidly worse, marked edema supervened at the level of abdominal wall and scrotum, the abdomen was markedly distended, and hemorrhages appeared where injections were given. The prothrombin time which had been normal before increased. A blood transfusion was started but the infant soon succumbed.

Autopsy revealed atelectasis and hyperemia, particularly of the posterior lung portions. The abdomen was distended and tense and the peritoneal cavity contained a small amount of clear fluid. The peritoneum was smooth and shiny. Stomach, small intestine and ascending colon were dilated and tense by gas pressure. The appendix formed a corkscrew-like structure, located on the medial side of the cecum and the latter showed striking reddish brown discoloration but no fibrin coating on its serosa. The liver was of normal size and consistency, and its section was reddish brown. The spleen was of normal size and consistency and its section was dark red. The other organs were normal. Histologic examination showed mucosal necrosis and abundant leukocytic wall infiltration in the apical portion of the appendix the lumen of which was filled with leukocytes. The diagnosis was acute phlegmonous appendicitis.

# Symposium Section

## Air Pollution

Up to the last few years of the last century the influence of air pollution in the production of disease in humans was considered a potent factor. For example physicians of that period seriously thought that the noxious effluvium which was believed to emanate from putrescent matter and float in the air as night mists was the cause of the prevailing fevers particularly in swampy areas. These nocturnal mists were called a miasma which arose from marshes. This miasma was believed to contain the necessary means of transmitting most of the febrile maladies to those who ventured out of doors after sundown. Amulets were worn by all who had to go out into the night, but instead of the usual charms these were in the nature of small bags of camphor, asafetida, garlic and other malodorous concoctions which were worn by a string around the neck. No satisfactory explanation of what these objectionable odors were expected to accomplish can be found but it is conceivable that they were intended as a counter-attack on the noxious miasma. Maybe they were intended to discourage those demonic little beings of the mist known in German mythology as Nibelungs, the original possessors of the famous hoard and ring won by Siegfried. It is understandable that they might select a less repellent atmosphere in which to indulge in their impish pranks. In any event the fevers continued in all areas near marshes whether they were located in tropical areas north or south of the equator or in the Fens of Lincolnshire or other English counties.

All of this fantastic, though fascinating, daydreaming was shaken to stern reality in 1901 when Walter Reed and his associates proved the theory, which Carlos Juan Finlay foreshadowed in 1891, that yellow fever is transmitted by a mosquito and when Sir Ronald Ross proved the malaria mosquito hypothesis of Sir Patrick Manson, in 1898. So the mischievous little Nibelungs which buzzed around in the misty miasma arising from the marshes after dark turned out to be mosquitoes with the less euphonious names of *Aedes aegypti* and *Anopheles maculipennis, Anopheles gambiae* and others. The first, of course, transmits yellow fever and the Anopheles group, malaria. To the present time, however, the term *paludism* is occasionally encountered to describe malarial disease and is derived from the word *paludine* or *paludal* from the Latin, meaning marsh. It is from this word that the recently synthesized drug *paludrine* derives its name.

The noxious effluvium which still arises from putrescent swamp decay and which constituted a very early example of air pollutions was also reduced in importance by the progress made in the bacteriologic origin of human disease. It still plays a part but, as far as is known at the present time, it contributes only indirectly.

With advances in our knowledge of specific bacterial causes of disease came the recognition that many of them could be air-borne. Perhaps the most frequent example is the common cold for which so many are spending so much for the best "plugged" pills that were ever passed "over the counter." This example of air-borne infection will remain high on the list just as long as ignorant or inconsiderate humans persist in sneezing in the subway or coughing in crowds without thoughtfully screening the really potent effluvium which they emanate quite visibly. Other common examples of air-borne diseases are measles, diphtheria, scarlet fever, tuberculosis and similar infections capable of circulating in the air from an infected host to a nearby contact. Then there is the transmission of disease entities by contaminated air through the inhalation of infected dust, sand particles, asbestos, bagasse, coal dust, cement, grain dust and other irritating occupational hazards. These may initiate definite lung pathology

in those who are not protected against inhaling them over a long period. They cause definite disease or morbid processes which are designated by adding the termination "-osis" to the specific substance which is responsible for them. Examples are silicosis, asbestosis and bagassosis. It is debatable at times whether these are true diseases or really morbid conditions or whether they are just lung injuries which prepare the tissue for the invasion of common pulmonary infections. Nevertheless, they cannot be excluded from pathologic processes due to air pollution.

These common examples have been accepted for years and measures to minimize them have been developed. Cubicles have been built in wards or sheets have been hung between beds where cross infection has been considered as being probable. Masks have been provided for those in hazardous occupations. Dry sweeping has been out for years. Vacuum cleaners have contributed toward reducing danger from household dust. The dangers of contact infections are more widely known by the public and there can be no doubt but that the diseases which are ordinarily transmitted by air pollution, such as has been suggested, are rapidly declining.

It took a rather dramatic episode to arouse interest in what proved to be rather tragic effects of another common form of air pollution. It will be recalled that this occurred in Donora, Pennsylvania, during the last week of October, 1948. The details were previously presented[1] but the recent report of the investigation[2] of the United States Public Health Service has reawakened interest in this dangerous and too common form of health hazard. Long before this happened in the small steel mill town on a curve of the Monongahela River in western Pennsylvania smoke had been recognized as a dangerous nuisance. Measures and laws had been enacted to abate this nuisance but for the most part their enforcement, like many others, has been lax and has been confined to large cities like St. Louis and Pittsburgh. Even in these localities it has been difficult to subordinate prosperity to the pollution of the surrounding atmosphere. Maybe some recalled that a couple of decades ago too many smokeless stacks were conspicuous against a perfectly clear background. But some progress has been made in minimizing and often arresting the smoke from busy industrial plants.

The location of such plants very often complicates the effectiveness of measures which have been developed and when smoke combines with fog to form what is now called "smog" the situation gets beyond control. In areas along waterways and near the seacoast smogs are common if smoke from industrial plants or from our annual preventable marsh and forest fires adds its part of the pollution. Smogs are common in the natural bowls between the hills and mountainous areas where plants are located and around Donora the atmospheric conditions last October were such as to cause an accumulation of smoke and fog which was unusually severe and persistent. It began on Wednesday of this memorable week and by Saturday the first death occurred. Before the atmosphere became clear again, 43 per cent of the 13,839 persons in the area were affected by an irritation of the respiratory tract and the predominant symptom was, of course, coughing.

Broken down statistically, 15 per cent were mildly affected according to the U.S. P.H.S. survey and the observations of Dr. Clarence A. Mills[3] of the College of Medicine of the University of Cincinnati, who has long been an authority on climatology. The percentage affected rose rapidly with age, was greatest at higher levels than down along the river and was actually highest across the river from Donora in Webster. Other figures are that 17 per cent were affected moderately and 10 per cent severely. Over 60 per cent of persons 65 years of age and older were among those affected and almost half were among the severely affected group. Although the onset in some cases was as early as the first day of the severe smog, 40 per cent occurred on the second day and by the end of the third day 17 persons had died. Three more died shortly after and brought the total number of deaths to 20.

1. Editorial: Smog Deaths, *Internat. M. Digest*, **54**: 59 (January) 1949.
2. U. S. P. H. S.: Air Pollution in Donora, Pennsylvania, *Pub. Health Bull.*, No. 306.
3. Mills, C. A.: The Donora Episode, *Science*, **111**: 67 (January 20) 1950.

The average age of those who died was 65, the youngest being 52 and the oldest 84. As was to be expected from this observation cardiac and/or respiratory disease was a predisposing factor in determining the severity of the smog symptoms as well as the mortality.

Attention is called to the fact that we have written that it took the dramatic episode of Donora to *arouse* and *reawaken* interest in the health hazards of air pollution, especially as it occurred in this Monongahela valley town. So any implication that a *new* health hazard has been discovered is not in accord with observations made long before this tragedy. For example we reported[1] a strikingly similar episode which was editorially mentioned by the *Lancet* when they discussed the Donora deaths last year. It happened in the valley of the Meuse River on the European continent. On this occasion 63 people died under the same circumstances which killed the 20 in the valley of the Monongahela. They likewise occurred in a period of a little more than 24 hours. The area involved was about 25 kilometers long in the valley south of Liége in Belgium and extended inland for about ½ kilometer on each side of the river. While the investigation of the Donora episode by Mills and by the U.S.P.H.S. was more thorough than is recorded concerning the one in the Meuse valley, sulfur dioxide from zinc plant sintering operations was a predominant noxious gas in both instances. Further in support of our impression that the Donora incident merely awakened interest in air pollution, of which it was a dramatic demonstration, is the fact that years of work by others in this country seems to have been overlooked. Moreover, it seems reasonable at least, to believe that the deleterious effects of smog alone have been appreciated by medical men for years even though the gases which it is certain that it contains are not as toxic as when the output of the stacks of industrial plants increase them to the extent that they are unsafe to animal life. It is logical to expect that when humans live in a rather concentrated atmosphere of smog for any length of time they do acquire some degree of anoxia. It is, likewise, conceivable that the carbon monoxide content of the blood will increase because in the smoke part of the fog this gaseous product of incomplete combustion is bound to be abundantly present.

In some accounts of what happened in Donora it has been implied that a new field of investigation has been opened up but as has been suggested this must be due to what we like to call a failure "to drink deeply of the Pierian spring" of medical literature. We are reluctant to think that it was one of those too often occurring instances of what Homer F. Swift[4,5] mentioned in his recent Kober Lecture on the Etiology of Rheumatic Fever: "Relative indifference to the information that has been laboriously collected and correlated."

As has been mentioned, Dr. Clarence A. Mills of the College of Medicine of the University of Cincinnati has been an authority on the effects of atmospheric conditions on human health for years. The recognized name for this, as far as these conditions are influenced by climate, is climatology. But it has progressed beyond that and Dr. Mills has been responsible for no small part of this progress. Naturally he was interested in the Donora episode and conducted an early investigation of his own. Among many observations made by all investigators, some of his deductions and interpretations reflect what happened at Donora to cause the deaths and what may prove to be the impairment of the health of many.

Months were spent by the U.S.P.H.S. investigators in analyzing the valley air for poisons but Mills suggests that the results were underevaluated. This he based, for a single example, on the previous observation that the very irritating red oxides of nitrogen, which are among the many industrial gases from acid plant stacks, very likely reached concentrations almost as high as had been set as the maximum allowable for safety of factory workers exposed only for an eight hour work day. It is also logical to assume that all noxious gases from industrial stacks reached concentrations far beyond allowable limits within the plants during the four days of blanketing smog.

4. Swift, H. F.: The Etiology of Rheumatic Fever, *Ann. Int. Med.*, **31**:715 (November) 1949.
5. Editorial: Etiology of Rheumatic Fever, *Internat. M. Digest*, **56**:118 (February) 1950.

Another of the many observations which will be discussed and analyzed was the effects on lower animals and vegetation. The effects on animals were similar to those on humans but the denuding of vegetable life and the consequent erosion usually seen around smelters was notable at Donora. Again it may be said that this has long been recognized as a common occurrence around smelters of copper or zinc. It was emphasized in the Meuse valley episode.

One observation which was made in the Meuse valley, which illustrates that there are still many factors which may be health hazards to be studied, is that there was an inordinate amount of fluorine in the smoggy air. It was so concentrated that it was a common observation that the electric light bulbs lost their transparency. They became frosted by effects of the fluorine on glass. It is easy to confirm this in many industrial plants, mines, smelters, foundries, etc. where the air is polluted even to a degree far below that reached at Donora or in Belgium.

It may not be possible to prevent another Donora tragedy, but from what was known before it happened together with what was learned from it we are in a position better to protect the population who must live in these hazardous areas. Atmospheric conditions have been rendered less noxious in other areas by the effective use of methods minimizing gases emitted from stacks. Smoke nuisances have been overcome in many cities and it is possible to burn carbon monoxide into carbon dioxide as a fuel-saving measure. So while the Donora deaths have not opened a new field in preventive medicine, it apparently has awakened the responsible authorities to the need for more generally enforcing the use of the established measures of control while they are trying to find bigger and better ways of saving human life in gas bowls like Donora.

In the preliminary report of the U.S. P.H.S. the importance of continued study is clearly shown and Congress has been asked to appropriate the modest sum of $750,000 to finance it. Would it not be unthinkable to have this request drowned in the maelstrom of the oratory to determine the size of the appropriations to develop bigger and better ways of destroying human life.

# International Medical Digest

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### "Burr" Red Blood Cells

For many years after the red blood count became an indispensable aid in the diagnosis and classification of anemias the terms anisocytosis and poikilocytosis were considered adequate to convey the information that the red cells were malformed and irregular in size and shape. The first term means that the cells are dissimilar in that they are inequal in size in all dimensions and when their color varies the term anisochromatic is used to describe the unequal amount of hemoglobin they contain. When the red cells are malformed and oversized they are referred to as poikilocytes. Soon, however, hematologists began further to subdivide irregular and malformed cells and demonstrated that they were important in the diagnosis of the anemias which were likewise being classified.

Aside from their study of erythropoiesis from the endothelial cell through its stages of megaloblast, erythroblast, normoblast, reticulocyte and finally an erythrocyte, they were interested in its appearance after it reached this latter stage when it was supposed to be fully developed. It was soon realized that a supposedly fully developed erythrocyte could change into many bizarre shapes and sizes and more descriptive terms than the two general terms above were needed. Soon there were many suggested and they were inspired by the imagination of hematologists and technicians. It is, therefore, understandable that several terms to describe the same type of cell have been brought forth. Many have survived because their significance was established after orderly study.

A few which may be cited to illustrate are the sickle-shaped cell which causes the anemia still believed to be confined to the Negro race in which there also exists the hereditary trait towards sickling of the red cells. This latter tendency does not always cause anemia and often there may be a predominance of such cells in the blood so that sicklemia is the term used. Then there are the thin red cells in which the biconcave surfaces probably meet in the center with the result that light passes through. These cells are called target cells, because the translucent centers surrounded by a red periphery of whatever hemoglobin remains in them strongly suggests a conventional target. The erythroblastic anemia first described by Cooley in 1925 is one of the anemias in which these cells may be seen and which has since been demonstrated in many races besides those inhabiting the Mediterranean Riviera.* There are other odd-shaped red cells which could be cited which have been more or less indicative of different anemias.

The latest to be described is the "burr"-shaped cell which Schwartz and Motto[1] of the Hematology Laboratory and the Hektoen Institute for Medical Research of the Cook County Hospital noticed in large numbers in some blood films which they were routinely reviewing with many others. The point which their report seems to emphasize is that they gained the impression that this malformed erythrocyte was frequently encountered in uremia, carcinoma of the stomach and peptic ulcer with bleeding. The "burr" cell is a mature erythrocyte about 7.5 microns or less in diameter having one or more spiny projections from its periphery. The name was selected because of its resemblance to the prickly projections surrounding burrs. What causes red cells to get this way is not known. Severity of anemia, duration of bleeding, degree of nitrogen retention, dehydration, age, sex and race were all considered and rejected by these observers, although they believe they may eventually

* See page 167.

1. Schwartz, S. O. and Motto, S. A.: The Diagnostic Significance of "Burr" Red Blood Cells, *Am. J. M. Sc.*, **218**:563 (November) 1949.

become significant signs in the study of anemia. They are rare in normal bloods (none in 100 controls). The diagnosis of the conditions in which Schwartz and Motto observed these "burr" cells has been well established but they have described a cell for which others should be alert. Maybe others have seen them but if so they must have kept it to themselves, so far as we know. After all it is not difficult to see them as they are quite apparent in the illustrations used in the report. We can use all the reliable diagnostic aids which can be developed and it is to be hoped that the presence of the "burr" cell in blood films may prove to be a new one.

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## Arctic Poliomyelitis

In the epidemiology of communicable diseases seasonal incidence has long been considered important. Under ordinary circumstances it is, with some limitations, a reliable guide as to what may be expected to prevail over the period of a year. It serves as an aid to public health workers planning the use of preventive measures and helps the practicing physician by alerting him as to what he may expect from month to month. It has long been known that seasonal temperatures are by no means the sole factor in the prevalence of these diseases but the general realization of this has been awakened only rather recently. The average practicing physician knows quite well that the atypical is to be expected at all times but recent discussions have caused him to look for the unexpected as a routine part of diagnostic procedure. A striking example of this was the unusual prolongation of the poliomyelitis prevalence of last year when the number of cases was exceeded only once before in the United States, in 1916. Of even greater interest was to read[1] of two outbreaks which occurred in isolated Eskimo communities in the Arctic regions of Canada during the winter of 1948 to 1949, which was one of the coldest ever known.

Ordinarily it is during this season of the year that we of the temperate zones take stock of what may have been learned about the disease and prepare to meet the outbreak which we have come to know may be expected in the spring. Even though there is ample precedent for variations in the seasonal prevalence of the communicable diseases which we, of the civilized world, have introduced to previously happy and contented natives of the Arctic, these two outbreaks are of more than ordinary interest. The communities involved are on the western coast of Hudson Bay and inland between latitudes 60 and 65 degrees N., which is as cold as any part of the Arctic mainland and feels colder because of the constant winds. In this severe winter the temperature fell to −49° F. In the first outbreak, which affected a group of trading posts with a combined population of 500 Eskimos, between September 1948 and March 1949, there were 21 cases with paralysis and 4 deaths. In the second outbreak, a trading post farther north, in February (the coldest month of the winter) there were 39 cases with paralysis and 14 deaths among a population of 275; including the nonparalytic, the attack rate was at least 50 per cent. Poliomyelitis was probably introduced into these Eskimo communities by ship from a military installation at Churchill 100 miles or so to the south, where a case with paralysis occurred in July 1948. The only known link between the first and the much more severe second outbreak was a missionary who arrived in Chesterfield 16 days before the first case there was recognized but who, so far as could be ascertained, had never been ill.

Low temperatures are used to preserve viruses in the laboratory, so it is reasonable to expect that they survived the temperatures which prevailed in these communities. There is ample precedent for this. The late John Toomey, whose passing will be a great loss to the study of poliomyelitis, with his associates[2] stopped a serious epidemic by promptly isolating the virus from creek water near the town of Perrysburg, Ohio, in 1945. There was reason to believe that the virus in this creek had

1. Adamson, J. D., Moody, J. P., Peart, A. F. W., Smillie, R. A., Wilt, J. C. and Wood, W. J.: Poliomyelitis in the Arctic, *Canad. M. A. J.*, **61**: 339 (October) 1949.

2. Toomey, J. A., Takacs, W. S. and Weaver, H. M.: Isolation of Poliomyelitis Virus from Creek Water by Direct Transmission to the Cotton Rat, *Am. J. Dis. Child.*, **70**:293 (November-December) 1945.

survived being frozen during the previous winter.

Let us recall that the seasonal incidence of infectious diseases is by no means constant to the north of the temperate zones. Peter Ludwig Panum's all-time classic report[3] of the famous epidemic of measles in the Faroe Islands in 1846 included the observations that when it was introduced after a lapse of 65 years it spread to a highly susceptible population and did not stop until all nonimmunes had been affected. Similar observations made by Dungal[4] in Iceland in an epidemic of measles starting in May 1943 corroborated this. So the unseasonable prevalence of poliomyelitis in these Arctic communities may be attributed to the resistance of the virus to low temperatures and the mass susceptibility of the inhabitants. Maybe it is just another example of the influence of immunity and susceptibility on the periodicity of epidemics, their duration and in bringing them to a close.

3. Panum, P. L.: Maeslinge-Epidemien paa Faeroerne 1 Aaret 1846, *Bibliot. f. laeger* (Copenhagen) 3R, **1**:270, 1847. Beobachtungen über das Maserncontagium, *Virchows Arch. f. path. Anat.*, **1**: 492, 1847. (This classic is available in an English translation from the original Danish by Ada Somerville Hatcher and is obtainable from the American Public Health Association, 1790 Broadway at 58th Street, New York 19, New York.)

4. Dungal, N.: Convalescent Serum Against Measles (in Iceland), *J. A. M. A.*, **125**:20 (May 6) 1944.